EDITED SUBMISSIONS RECEIVED IN RESPONSE TO THE NOTICE INVITING SUBMISSIONS ON MATTERS REFERRED TO THE:

Advisory Committee on Chemicals Scheduling – 22 February 2011 (ACCS#1);
Advisory Committee on Medicines Scheduling – 23 February 2011 (ACMS#2);
and
Joint Meeting of the ACCS and ACMS – 28 February 2011 (ACCS-ACMS#2);

Regulation 42ZCZL, Therapeutic Goods Regulations 1990 (the Regulations)

A delegate of the Secretary of the Department of Health and Ageing publishes herein all public submissions made in response to the invitation contained in the notice inviting public submissions for ACCS#1, ACMS#2 and ACCS-ACMS#2 (the February 2011 meetings). Please note that, for the February 2011 meetings, there was an additional supplementary invitation notice and any submissions in response to this are also published here. Both invitation notices, with closing dates of 19 January and 21 January 2011 respectively, are accessible at www.tga.gov.au/regulation/scheduling-adv-com.htm.

In accordance with the requirements of subsection 42ZCZL of the Regulations these submissions have been edited to remove information that a delegate considers to be confidential.

As advised in the notice inviting public submissions, it was up to the person making the submission to highlight any information which they wished to request be considered as confidential. Material claimed to be commercial-in-confidence has been considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework (SPF), issued by the National Coordinating Committee on Therapeutic Goods. The SPF is accessible at www.tga.gov.au/regulation/scheduling-policy-framework.htm.

Discrete submissions have been grouped by item. However, a number of applicants provided submissions that related to multiple items. These submissions on multiple items have been separately grouped.

LIST OF SUBMISSIONS

1. ACCS #1

Two submissions were received. These were both submissions relating to the consideration of diethylhexyl phthalate.

2. ACMS #2

Item	Number of public submissions
2.1.1 Chloramphenicol	1 (and in 1 submission under item 2.3)
2.1.2 Fexofenadine	6 (and in 1 submission under item 2.3)
2.1.3 Ibuprofen	2 (and in 1 submission under item 2.3)
2.1.4 Ibuprofen combined with paracetamol	4 (and in 1 submission under item 2.3)
2.2.2 Pantoprazole	10 (and in 1 submission under item 2.3)
2.2.3 Rupatadine	1
2.2.5 Tolvaptan	4
2.3 Submissions on multiple matters	1

3. ACCS-ACMS #2

Three submissions were received on the one matter before ACCS-ACMS#2 – consideration of methylsulfonylmethane / dimethyl sulfone.

1.3 Diethylhexyl phthalate - submission 1/2

[redacted]

[redacted]

[redacted]

19 January 2011

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Dear Secretary

[redacted]position on proposed amendments to the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) as they relate to Diethylhexyl phthalate (DEHP) in toys and childcare articles

We have recently become aware of an invitation for public comment regarding proposed amendments to the SUSMP, in particular, proposed amendments to the limit on Diethylhexyl phthalate (DEHP) (2.3) in toys and childcare articles. The relevant clause is outlined below:

> 2.3 Diethylhexyl phthalate (DEHP) - proposal to schedule DEHP, including consideration of:
>
> - a parent entry in Schedule 6 or 7;
> - prohibition of cosmetic use through listing in Appendix C.
>
> The delegate is also seeking advice on potential cut-offs and exemptions, including possibly restricting the use in toys and childcare articles to less than 0.05 per cent.

As you may already be aware, on 2 March 2010, following recommendations by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), an interim ban on *Children's plastic products with more than 1 per cent DEHP* came into effect by way of **Consumer Protection Notice No.6 of 2010** (see **Attachment A**).

This interim ban prohibits supply of certain plastic products that:

- are intended for use by children up to and including 36 months of age;
- contain or have an accessible component containing more than 1 per cent by weight of DEHP;
- are products that children up to and including 36 months of age can readily chew and/or suck.

This limit is based on the NICNAS Priority Existing Chemical Assessment Report No.32 on Diethylhexyl Phthalate (July 2010). The NICNAS assessment found that a risk of

reproductive toxicity exists for young children in certain circumstances, and determined that the risk applies to young children up to and including 36 months of age who may extensively chew and suck (mouth) objects on a recurrent basis for substantial periods of time—in excess of 40 minutes per day.

The NICNAS study also found:

- the risk does not apply to older children or adults, who have less substantial mouth contact with plastic materials that contain DEHP
- skin contact with products containing DEHP is not a safety concern for any age group, including infants.

The report can be accessed at:
http://www.nicnas.gov.au/Publications/CAR/PEC/PEC32/PEC_32_Full_Report_PDF.pdf.

On 1 January 2011, the new Australian Consumer Law (ACL) provisions came into effect which introduced a new nationally consistent system to regulate the safety of consumer goods and product related services. In relation to unsafe goods notices (or interim bans) of this type which were declared under the previously named *Trade Practices Act 1974* (TPA) and were still in force on 1 January 2011, the interim ban continues in force as if it were an interim ban imposed under the ACL. In addition, the current ban on Children's plastic products with more than 1 per cent DEHP is in the process of being made a permanent ban under the ACL and is expected to be completed by March 2011.

In relation to proposed amendments under the SUSMP, the proposed limit of 0.05 per cent in respect of toys and childcare articles is clearly inconsistent with the ACCC's current ban on goods containing more than 1 per cent DEHP. [redacted] is of the view that an amendment to the SUSMP to restrict the use in toys and childcare articles to less than 0.05 per cent DEHP will raise significant compliance issues with suppliers, and cause safety concerns amongst consumers regarding these products. As part of its obligations under the TPA, the ACCC conducted a conference with industry members in February 2010 to discuss the proposed ban. The current ban now in force reflects industry comments arising from that conference.

Subject to further risk assessments conducted by NICNAS on DEHP which support a change to the DEHP limit on toys and childcare articles to 0.05 per cent, [redacted] current position is that the present limit of 1 per cent is adequate.

If you have any queries, please do not hesitate to contact [redacted].

Yours sincerely

[redacted]

ATTACHMENT A

COMMONWEALTH OF AUSTRALIA

TRADE PRACTICES ACT 1974

Consumer Protection Notice No. 6 of 2010

DECLARATION THAT CERTAIN GOODS CONTAINING MORE THAN 1% DIETHYLHEXYL PHTHALATE (DEHP) ARE UNSAFE GOODS

I, CRAIG EMERSON, Minister for Competition Policy and Consumer Affairs, pursuant to section 65C(5) of the *Trade Practices Act 1974* **DECLARE** goods of the kind specified below to be unsafe goods:

Particulars of goods:

a) Toys;
b) childcare articles including, but not limited to, dummies, pacifiers, teething rings, teething rails, rattles, bibs, gum soothers, and comforting objects; and
c) eating vessels and utensils including, but not limited to, feeding bottles, sip/sucking cups, bowls, plates, and cutlery

that:

d) are intended for use by children up to and including 36 months of age;
e) contain, or that have a component which contains, more than 1% by weight of the chemical identified by the unique Chemical Abstract Service (CAS) Number 117-81-7 (also know as Diethylhexyl phthalate (DEHP), Di(2-ethylhexyl)phthalate and Bis(2-ethylhexyl)phthalate); and
f) are, or have a component containing more than 1% by weight of the chemical identified by the unique Chemical Abstract Service (CAS) Number 117-81-7 that is, readily able to be sucked and/or chewed by children up to and including 36 months of age;

but excluding

g) clothing and footwear;
h) sporting goods;
i) floatation aids and aquatic toys for the specific purpose of assisting a supervised child to float or swim in water; and
j) second hand goods.

Dated this 26th day of February 2010

CRAIG EMERSON
Minister for Competition Policy and Consumer Affairs

1.3 Diethylhexyl phthalate - submission 2/2

Diethylhexyl Phthalate - DEHP
(Di(2-ethylhexyl)phthalate; CAS NO: 117-81-7)

Introduction

DEHP was declared a Priority Existing Chemical (PEC) under the *Industrial Chemicals (Notification and Assessment) Act 1989* (ICNA Act, 1989) based on the actual and potential use of DEHP in toys, child care articles and cosmetics. A public health risk assessment associated with these applications was conducted by NICNAS. The final report is available from the NICNAS website at: http://www.nicnas.gov.au/Publications/CAR/PEC/PEC32/PEC_32_Full_Report_PDF.pdf

Information provided by industry to NICNAS indicates that DEHP is imported as a raw material that could be used in toys, childcare articles and/or cosmetics. Importation of perfumery and cosmetic products containing DEHP was also indicated. In Australia DEHP is mostly used, for industrial purposes, as a plasticiser in PVC and in other polymers for coatings, adhesives and resins.

Currently in Australia there are no restrictions on the use of DEHP in cosmetics. The use of DEHP in certain toys and childcare articles has been limited to up to 1% under section 65 of the Trade Practices Act 1974 (TPA) following the PEC assessment recommendation. A temporary 18 months ban effective 2 March 2010 is now in place. The products subject to the temporary ban are those intended for use by children up to and including 36 months of age, where they contain more than 1% DEHP. These products are toys and childcare articles where significant mouth contact may occur. The interim ban in Australia is in the process of being made a permanent ban under the new Australian Consumer Law (ACL) provisions that came into effect in January 2011. The process is expected to be completed by March 2011. The Australian ban is consistent with the current restrictions on use of DEHP in toys and childcare articles in EU, USA and Canada, although Australia has adopted a higher concentration limit of 1% compared to 0.1% limit in the other countries with restrictions.

Current EU legislation prohibits the use of DEHP in cosmetic products under the Cosmetic Directive (Article 4b of the Cosmetic Directive 76/768/EEC, introduced in 2004) based on the restrictions for cosmetic use of chemicals with known carcinogenic, mutagenic or reproductive (CMR) toxicity. In the USA, use of DEHP in personal care products was prohibited by state legislation in California. In Canada, DEHP was added to the Health Canada List of Prohibited and Restricted Cosmetic Ingredients (The Cosmetic Ingredient Hotlist) as of September 2009. There are no regulatory restrictions on the use of DEHP in cosmetics in Asia and other non-EU other countries.

Kinetics and Toxicity Profile

DEHP is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration. Based on a number of studies, majority in animals, the bioavailability of DEHP via the oral route is estimated to be 100% in both adults and children. Absorption of DEHP via the skin is significantly lower. The extent of dermal absorption in vivo was determined to be about 9% and 26% in rats and guinea pigs, respectively. Comparison studies in vitro demonstrate that human skin is significantly less permeable (4-fold) to DEHP than rat skin. Therefore, bioavailability of dermally applied DEHP in humans is not likely to exceed 5%.

Case studies of transfusion and haemodialysis patients and occupationally exposed workers indicate absorption of DEHP can occur via both inhalation and parenteral routes, however, quantitative data for absorption of DEHP via the respiratory tract are not available. A substantial proportion of DEHP in aerosols may also become bioavailable via the gastrointestinal tract rather than the respiratory tract. The bioavailability of DEHP via the inhalation route in humans is estimated to be 100%.

Studies in rats and monkeys show the liver, kidney, testes and blood as the main sites of distribution following orally administered DEHP, however, DEHP and metabolites do not accumulate in tissues.

DEHP and/or its metabolites have been detected in foetal tissues demonstrating that they can cross the placenta.

The first metabolic step is the hydrolysis of DEHP to monoethylhexyl phthalate (MEHP) and 2-ethylhexanol (2-EH) by tissue lipases. MEHP is further metabolised via oxidative reactions resulting in the formation of numerous metabolites and a small amount of phthalic acid. Elimination of metabolites and minimal quantities of the parent DEHP occurs mostly via urine and faeces. A recent human study noted that 75% of orally administered DEHP was eliminated as metabolites via urine within 2 days.

Acute toxicity

In experimental animals, DEHP exhibits low acute oral, dermal (LD50 >5000) and inhalation toxicity (LC50 > 10.62 mg/L in the rat (4h exposure)). Intravenous and intraperitoneal administration of DEHP results in higher acute toxicity than oral or dermal administration, however, the acute toxicity via these routes is still low. Therefore, DEHP is expected to have low acute toxicity in humans.

Irritation and sensitisation

DEHP induced minimal skin and eye irritation in animals and did not induce skin irritation in human volunteers. Data are insufficient to determine the respiratory irritation potential of DEHP. In animal studies DEHP is not a skin sensitiser and limited data indicate no sensitisation reactions in humans. Human studies indicate correlations between the risk of bronchial obstruction and plasticiser-emitting components of the indoor environment. However, there is currently insufficient evidence supporting a causal relationship between respiratory effects and DEHP.

Repeat dose toxicity

The repeated dose toxicity of DEHP has been evaluated in a number of animal species, in both short-term (few weeks) and life-time studies by several routes of exposure. The most pronounced effects are on the liver (hepatomegaly, peroxisome proliferation), kidney (increased organ weights, mineralisation of renal papilla, tubule cell pigments and chronic progressive nephropathy) and testes (atrophy, vacuolated Sertoli cells, multinucleated gonocytes, Leydig cell hyperplasia).

Exposure to DEHP during gestation and sensitive age post-natal periods in rodents also causes significant effects on reproductive parameters and development.

Liver effects

Liver effects were reported in several rodent species. In rats, hepatotoxicity was indicated by significant increases in serum albumin, absolute and/or relative liver weights and peroxisome proliferation at 146.6 mg/kg bw/d and above. The NOAEL for these effects was 28.9 mg/kg bw/d. A similar NOAEL, 25 mg/kg bw/d, was established based on hepatic changes after sub-chronic intravenous exposure in rats. The liver effects induced by oral administration of DEHP in rodents were not reported in oral administration studies with marmoset monkeys.

Studies with knockout mice have shown that the liver effects induced by DEHP in rodents (hepatomegaly, peroxisome proliferation) are largely mediated through activation of peroxisome proliferator-activated nuclear receptor alpha (PPARα). In other species, such as Syrian hamsters, guinea pigs and monkeys, activation of PPARα by DEHP was significantly lower or not observed.

Studies with hypolipidaemic agents in humans have provided no evidence of peroxisome proliferation or increased hepatocyte division. Overall, the mechanisms by which DEHP and other peroxisome proliferators induce chronic hepatotoxicity in rodents are not considered relevant to humans.

Kidney effects

DEHP-associated toxicity was consistently observed in kidneys of rats and mice. A LOAEL for these effects is established at 146.6 mg/kg bw/d from a 104-week rat dietary study, based on increased absolute and relative kidney weights. Mineralization of renal papilla, tubule cell pigmentation and chronic progressive nephropathy was observed at higher doses. The NOAEL for kidney effects is 28.9 mg/kg bw/d.

No information related to kidney toxicity is available in monkeys.

Human studies on DEHP-induced toxicity to kidneys are not available.

The mechanism of DEHP-related toxicity to kidneys is not clear but it appears that it is not related to peroxisome proliferation as kidneys lesions were found in both PPARα-null and wild-type mice.

Given the lack of information on DEHP-induced kidney toxicity in primates (including humans), the relevance to humans of kidney effects observed in rats cannot be excluded.

Testicular effects

Testicular toxicity of DEHP in repeated dose studies in rats manifests as decreased weights and testicular atrophy, increased bilateral aspermatogenesis, immature or abnormal sperm forms, seminiferous tubular degeneration, Sertoli cell vacuolation or complete loss of spermatogenesis. In a 13-week rat dietary study, a LOAEL of 37.6 mg/kg bw/d was established based on an increased incidence of Sertoli cell vacuolation. Significantly decreased absolute and relative testicular weights, mild to moderate seminiferous tubule atrophy and Sertoli cell vacuolation were observed at higher doses. The NOAEL was 3.7 mg/kg bw/d.

The consistent finding of testicular effects in rats and mice is in contrast to those from studies in marmosets where no significant treatment-related changes in testicular histology or more gross parameters were observed from oral exposures to DEHP of up to 2500 mg/kg bw/d. However these studies are limited in number and may not cover critical windows for testicular toxicity especially in young and developing animals.

Therefore, although there were no reports of DEHP-induced testicular toxicity in primates, the relevance to humans of the effects observed in rats cannot be excluded based on the plausible mode of action (discussed in detail below).

Genotoxicity

DEHP has been tested in a variety of short-term genotoxicity assays with predominantly negative results. Overall, DEHP is regarded as non-genotoxic.

Carcinogenicity

In long term studies DEHP exposure is associated with several types of tumours which involve different nongenotoxic mechanisms of carcinogenicity.

Hepatocellular tumours

In mice and rats, DEHP induced significant dose-dependent increases in the incidence of hepatocellular tumours. At low doses, there was no evidence of liver toxicity or increase in hepatocellular tumours, suggesting a threshold for this effect. The LOAEL and the NOAEL for tumour induction in rats were established as 146.6 mg/kg bw/d and 28.9 mg/kg bw/d, respectively. In mice, the LOAEL and the NOAEL for induction of liver tumours were 292 mg/kg bw/d and 98 mg/kg bw/d, respectively.

The evidence suggests that, similar to chronic hepatotoxicity, peroxisome proliferation combined with suppression of hepatocellular apoptosis could be the major mechanism for DEHP-induced hepatocarcinogenicity in rodents.

There are no reports of association between DEHP exposure and liver neoplasms in humans.

Overall, the mechanisms by which DEHP and other peroxisome proliferators induce chronic hepatotoxicity and hepatocarcinogenicity in rodents are regarded as not relevant for humans.

Mononuclear cell leukaemia

Mononuclear cell leukaemia (MCL) was reported in one of two rat carcinogenicity studies and in neither of two mouse carcinogenicity studies. Spontaneous occurrence of this tumour type is well known with high incidence in F344 rats and is rare in other rat strains. This neoplasm has not been found in other mammalian species and has no histologically comparable tumour type in humans.

Therefore, DEHP-induced MCL observed in rats is not considered relevant for humans.

Leydig cell tumours

In a single lifetime dietary study with Sprague-Dawley rats, DEHP was associated with increased incidence of Leydig cell tumours. In this study, the NOAEL for both hepatic tumours and testicular tumours was determined to be 95 mg/kg bw/d, based on the statistical significance of the observations at the high dose of 300 mg/kg bw/d. The dose-related trend of increased Leydig cell tumours was observed commencing from the lowest dose of 30 mg/kg bw/d.

Leydig cell tumours were not reported in other studies with F344 rats even at higher doses. Notably, spontaneous Leydig cell tumours are not common in Sprague-Dawley rats in contrast to F344 rats. DEHP does not appear to induce testicular neoplasias in B6C3F1 mice.

The involvement of PPARα in DEHP-mediated testicular toxicity, including Leydig cell hyperplasia, is not considered very likely based on the occurrences of testicular toxicity in PPARα-null mice. In addition, several other phthalates that activate PPARα were not associated with testicular toxicity, suggesting that hepatic and testicular toxicity are mediated through different pathways that may under some circumstances share common cofactors or targets depending on their tissue distribution.

Studies related to DEHP-induced testicular carcinogenicity in humans are limited and contradictory. A single occupational case-control study suggested an increased risk of testicular cancer from DEHP in the PVC industry. However, a larger follow-up study did not support this finding.

The mechanism for induction of Leydig cell tumourogenesis by DEHP in rodents is non-mutagenic and it is most likely related to perturbations in the levels of luteinizing hormone (LH) and/or modulated Leydig cell responsiveness for LH-mediated processes, such as steroidogenesis, i.e. interference with the regulatory pathways within the hypothalamic-pituitary-thyroid (HPT) axis. However, available data are inadequate to determine a reliable NOAEL for DEHP-induced Leydig cell tumours.

Toxicity to reproduction

Perturbations of testes structure and function are consistently observed in chronic studies with rodents examining the general toxicity of DEHP. In addition, numerous experimental animal studies, mostly using oral administration in rats, have been conducted to specifically examine the effects of DEHP on different reproductive parameters.

Fertility

For effects on fertility, a NOAEL of 14 mg/kg bw/d is derived from a continuous breeding study exposing both male and female adult CD-1 mice to DEHP via diet. The LOAEL was 140 mg/kg bw/d based on decreased litters and viable pups. At this dose, no significant histological effects were observed. However, at higher doses, decreased weights of male reproductive organs including testes, epididymes, prostate and seminal vesicles, bilateral atrophy of the seminiferous tubules, decreased sperm motility, sperm concentrations and complete infertility were evident. Decreases in fertility outcomes were not necessarily linked only to male infertility. A cross-over mating trial with untreated animals at the highest dose of 425 mg/kg bw/d showed that both sexes were affected by exposure to DEHP.

Continuous breeding dietary studies in rats also demonstrated effects on fertility and development of offspring. No NOAELs for fertility or development were established in the study where Sertoli cell vacuolation was observed in F1 offspring from the lowest dose level of 113 mg/kg bw/d. In another two generation study in rats adverse effects on fertility were observed in the F0 adults at 592 mg/kg bw/d and above, manifesting as decreased number of live pups per litter. At higher doses, histopathological effects on the testes were apparent. However, similar reproductive effects were observed at lower doses in F1 generation parents. For fertility effects, the NOAEL was 46 mg/kg bw/d and the NOAEL for developmental effects was 4.8 mg/kg bw/d (discussed further below).

For testicular histopathology related to Sertoli cell vacuolation, NOAEL and LOAEL of 3.7 and 38 mg/kg bw/d, respectively, were identified in a 13-week rat dietary study based on a dose-dependent Sertoli cell vacuolisation in male rats. At the highest dose of 375.2 mg.kg bw/d, bilateral, multifocal, or complete atrophy of the seminiferous tubules with complete loss of spermatogenesis was also seen.

Studies in rats suggest that DEHP-mediated fertility effects may also result from alterations in Leydig cell steroidogenesis, which are dependent on the age of the animal and the duration of treatment. Younger Long-Evans rats appeared more sensitive than older postpubertal rats for DEHP-related perturbations in Leydig cell steroidogenesis and serum levels of testosterone and LH. From these studies, a NOAEL of 1 mg/kg bw/d was established based on increased serum LH and testosterone levels in rats exposed to 10 mg/kg bw/d for 28 days during PND 21-48. This effect correlated with increased basal and LH-stimulated testosterone production ex vivo in Leydig cell preparations from these animals.

Testicular effects were not observed in studies of DEHP in marmoset monkeys. However, it is noted that the number of studies examining fertility effects in marmosets are limited.

In humans, available studies on fertility effects of DEHP are limited, generally examining correlations between urine levels of DEHP metabolites and male and female reproductive health. Overall, these studies do not identify significant associations between the metabolite MEHP and adverse semen parameters, hormone levels, time-to-pregnancy, or infertility diagnoses in adults. However, a single recent occupational study suggests that circulating testosterone levels are reduced in male workers exposed to DEHP and DBP.

Developmental toxicity

DEHP induces overt structural malformations (predominantly of the tail, brain, urinary tract, gonads, vertebral column and sternum) in rats exposed to 1000 mg/kg bw/d during the critical period of foetal development. More subtle effects, such as changes in anogenital distance (AGD), were also recorded in a number of other studies. Based on reduced AGD, a LOAEL of 113 mg/kg bw/d was determined in rats (the lowest dose tested which was not maternally toxic).

In a postnatal developmental study with Wistar rats exposed to DEHP during gestation and lactation (GD6 to PND21), a NOAEL for developmental toxicity was established at 1.2 mg/kg bw/d, based on increased testes weight in prepuberal rats at 5 mg/kg bw/d. These weight increases were not associated

with any histopathological or biochemical alterations. In a continuation of the study, a NOAEL for female developmental toxicity was established at 5 mg/kg bw/d, based on a significant delay in vaginal opening observed at 15 mg/kg bw/d in female offspring.

Overall, the critical study for developmental toxicity of DEHP is a 3-generational dietary study in Sprague Dawley rats where a NOAEL of 100 ppm (4.8 mg/kg bw/d) was established based on decreased testes weight and seminiferous tubule atrophy at 1000 ppm (14 mg/kg bw/d). At higher levels of exposure, decreased in utero survival, reduced AGD, undescended testes, retained nipples/areolae, incomplete preputial separation and disruption of spermatogenesis in the F1 and F2 generations were also observed.

Strain specific differences are noted in the incidence of specific developmental malformations from DEHP exposure in rats. The same dose of DEHP was associated with a higher incidence of epididymal malformations in Sprague–Dawley rats while gubernacular malformations were more prevalent in Wistar rats.

One study in marmoset monkeys suggested that increasing DEHP doses could be associated with delay in the onset of puberty in male marmosets. However, mean serum testosterone levels were highly variable, and minimal effects on testicular structure or function was reported. The NOAEL was the highest tested dose of 2500 mg/kg bw/d. The lowest tested dose was also relatively high 100 mg/kg bw/d. The exposure in this study was from 90–115 days (juvenile) to 18 months (young adulthood) and may not have been at the crucial age window for reproductive development in marmosets.

In humans, a number of studies have been conducted examining correlations between maternal MEHP levels and gestation length, onset of puberty and AGD. Overall, these studies do not provide convincing evidence of developmental effects from DEHP exposure in humans. This is related to the low power of studies due to small sample size, not representative sample (usually one study centre) and also uncertainties about the significance of the measured endpoints, for example AGD, as an indicator of developmental toxicity in humans.

Mode of action

Although DEHP appears to act as an anti-androgen in rodents, neither DEHP nor its metabolite MEHP displayed affinity for the oestrogen or androgen receptor in vitro, suggesting that DEHP is not an androgen receptor antagonist.

The majority of data on the reproductive toxicity of DEHP and other related phthalates supports a mode of action that includes effects on steroidogenesis and expression of genes critical for development of the reproductive system in rodents.

DEHP was shown to down-regulate testosterone production and/or alter mRNA synthesis for several proteins (StAR, Cyp11a1, Cyp17a1 and Insl3) involved in steroidogenesis and testicular development.

Toxicity to Sertoli cells through effects on proteins involved in cell cycle regulation is also indicated by some studies. In neonatal rats, DEHP down-regulated synthesis of the cyclin D2 mRNA and decreased Sertoli cell proliferation. In addition, alterations in communication between Leydig and Sertoli cells may also play a role in testicular and developmental toxicity. In vitro treatment of rat Sertoli cells with MEHP resulted in cell vacuolization, perturbations of the intercellular membrane structures and distribution of tight junction specific proteins.

The exact mechanism(s) underlying reproductive toxicity of DEHP have yet to be fully elucidated. However, studies consistently demonstrate that the mechanism(s) ultimately lead to interference with endocrine function and thereby influence sexual differentiation and function. Therefore, considering that the components of the postulated mode of action in rodents are applicable to humans, the reproductive toxicity of DEHP observed in rodents is regarded as relevant for humans.

Critical health effects relevant for human risk characterization

For kidney toxicity the most appropriate NOAEL for risk estimates is 28.9 mg/kg bw/d, identified in a 104-week dietary study with rats.

For reproductive toxicity, examination of the weight of evidence supports a NOAEL for fertility and developmental effects in the dose range of 1–10 mg/kg bw/d. Within this range, the most appropriate NOAEL for risk estimates in adults and children is 4.8 mg/kg bw/d, determined from a multigenerational dietary study.

Public Exposure to DEHP

NICNAS conducted an assessment of the exposure of the general public, specifically for use of DEHP in cosmetics and personal care products.

Cosmetics and personal care products

In cosmetic products, phthalates including DEHP are used as humectants (skin moisturisers), emollients (skin softeners), skin penetration enhancers, agents to prevent brittleness and cracking in nail polishes and sealants, antifoaming agents in aerosols, and solvents.

Information provided to NICNAS indicates that the use of DEHP in cosmetic and personal care products in Australia is limited. In 2006, one company reported import of DEHP as a component of finished cosmetics and fragrances at a typical concentration of 0.05%. Another company reported that import of personal care products containing DEHP was discontinued since 2004. DMP, DEP, DBP and DnOP are currently used, or have the potential for use, in these applications. DEP is by far the predominant phthalate used in cosmetics with current data showing the presence of DEP in all cosmetic product types.

Worldwide, the phthalates predominantly found in personal care and cosmetics products are diethyl phthalate (DEP) and dibutyl phthalate (DBP) (Hubinger and Havery, 2006*; US FDA, 2008). DEHP has also been found in products available in Korea at concentrations up to 18.3 mg/kg in perfumes and up to 25.1 mg/kg in nail polish (Koo et al., 2004). No information is available publically on the concentrations of DEHP in cosmetics or personal care products in countries that have no restrictions on the use of DEHP in cosmetics. Trace amounts of DEHP (up to 167 mg/kg or 0.0167%) were found in 14 of 36 perfumery products tested in the EU (Peters, 2005). It was suggested that the trace amounts in these products could be due to leaching during early stages of formulation from plastic manufacturing equipment (containers, pipes, pumps) or from plastic tubing as part of the packaged product (SCCP, 2007). Plasticised containers for cosmetic and personal care products may also represent a source of exposure to phthalates, including DEHP, through leaching of plasticiser from the container into the product. However, available limited data suggest that contamination of cosmetic products from DEHP leaching from packaging or during manufacture is likely to be at very low levels.

The limited information from overseas sources on DEHP in cosmetics may reflect the effect of the EU prohibition effective since 2004. However, in light of the absence of restrictions on use of DEHP in cosmetics in Australia and many other countries, it is not possible to assume that all products marketed in Australia meet the EU standards. DEHP, along with a number of other phthalates are listed in the International Nomenclature of Cosmetic Ingredients (INCI), a system of names for ingredients of cosmetics designed to help cosmetic formulators find information on cosmetic ingredients. The International Cosmetic Ingredients Dictionary and Handbook (Gottschalck & McEwen, 2006) also contains a number of phthalates and their functions and DMP, DEP, DBP and DEHP are all listed with functions as fragrance ingredient, plasticiser and solvent. These listings of DEHP indicate that DEHP can be used in cosmetics and personal care products. In addition, substitutability between phthalates with similar properties is possible with likely limits on the extent to which dissimilar phthalates can be

used. However, little information is available in open literature on substitutability of phthalates and in the absence of information to characterise these limits complete substitutability was assumed to undertake the exposure assessment for DEHP for the cosmetic use scenario.

The typical concentration reported in Australia cannot be used to determine the likely concentration of DEHP across a range of types of cosmetic product, for use in the exposure assessment. In the absence of sufficient information on the actual concentrations of DEHP in cosmetics in Australia, the assumption of complete substitutability of phthalates, discussed in the Report in Section 4.2.3, is used to give a plausible worst case estimate of exposure. Essentially, the exposure assessment scenario is based on the assumption that DEHP could replace all DEP currently used in cosmetics. Therefore the content of DEHP in cosmetic products for the purposes of exposure assessment was assumed to be similar to concentrations of DEP currently reported in different cosmetic product types in Australia as this provides a basis to estimate a potential level of exposure to DEHP from cosmetic use. The values and mathematical models used to calculate the internal exposure are described in detail in the full PEC DEHP report.

Essentially two routes of exposure are considered, inhalation exposure from use of perfumery products and dermal exposure from leave on, rinse of and perfumery products. Total estimated exposure to DEHP from cosmetic use is 154.7 μg/kg bw/day based on a "worst-case" scenario of daily use of all (leave-on, wash-off and spray application) cosmetic products, as outlined in the Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation (SCCNFP, 2003 and SCCP, 2006) and EU TGD (EC, 2003). Additional assumptions are as follows:

- DEHP content in cosmetics is similar to that reported for DEP in a limited number of cosmetic products in Australia
- Bioavailability of DEHP via the dermal route is 5% and via the inhalation route is 100%.

The calculated worst case DEHP exposure to cosmetics and personal care products is greater than the levels of the DEHP metabolite found in biomonitoring data due to the worst case assumptions used. However the estimates for use of a single cosmetic product such as body lotion are close to the 95th percentile and the maximum concentrations measured in large biomonitoring studies. This indicates that the worst-case exposure scenarios considered in this assessment are relevant for highly exposed individuals.

Exposure to DEHP from use of personal care products was also estimated specifically for children using a model previously developed by NICNAS (NICNAS, 2009). The model considers that the quantity of the product applied to whole body of a child or infant (e.g. body lotion and cream) can be estimated from the ratio of body surface area of the child or infant compared with that of adult. For children from 0 to 10 years, the difference between surface area to bodyweight (SA/BW) ratio is as follows: 2.3 fold at birth, 1.8 fold at 6 months, 1.6 fold at 12 months, 1.5 fold at 5 years and 1.3 fold at 10 years (SCCP, 2006). In the absence of specific use data for children the same number of applications of body lotion per day as in adults is assumed and maximum DEHP concentrations as in adult body lotion products. Total estimated exposure in the different children age groups is outlined in Table 2. The highest exposure of 61.7 μg/kg bw/day is estimated for newborns. For children 6 and 12 months of age the estimated exposure is 48.2 and 42.9 μg/kg bw/day, respectively.

Risk Characterisation

The content of phthalates, and therefore DEHP, varies significantly depending on the function it has in the particular product. The highest reported concentration is, 25%, in nail polish (plasticizer) and 2.5% in perfume spray (solvent), whereas the concentration in other products is significantly lower, 0.25% in body lotion and even lower for other products.

The main route of exposure to DEHP from use of cosmetics in the general population is through dermal contact. Inhalation exposure is also possible from products applied as aerosols. Oral exposure is considered negligible as current information does not indicate use of phthalates in products most prone to accidental oral ingestion such as toothpastes, mouthwashes, lipsticks and lip-glosses.

Given the low acute toxicity of DEHP and low skin and eye irritation and skin sensitising potential, the risk of acute adverse effects for consumers from use of DEHP-containing cosmetics is low. However, repeated exposure to DEHP is associated with kidney and reproductive toxicity and the margins of exposure (MOEs) for these effects are discussed below.

Table 1 below outlines the MOE calculations for estimated DEHP exposure from combined use of cosmetics and personal care products considering the total estimated exposure to DEHP of 154.7 μg/kg bw/day based on a "worst-case" scenario and the NOAELs for the critical health effects.

Table 1: Calculated MOE for critical health effects of DEHP from estimated exposure to cosmetic products for general population

Type of toxicity	NOAEL mg/kg bw/d	MOE for reasonable worst case exposure scenario
Reproductive	4.8	31
Kidney	28.9	187

The estimated MOE for reproductive toxicity in the general population is less than 100. This indicates that the risk for the general population of reproductive toxicity from simultaneous use of multiple cosmetic products containing DEHP is high. The low MOE of 31 and the nature of the reproductive toxicity with a potential for serious long term and irreversible effects for offspring indicate especially high risk for pregnant and breastfeeding women due to potential exposure to DEHP in cosmetics given the current absence of restrictions on DEHP use in cosmetics in Australia.

The risk estimate for chronic effects to kidneys derives a MOE above 187 indicating low concern for kidney toxicity in the general population using multiple cosmetic products containing DEHP.

Based on the exposure estimates in children the MOE for reproductive effects due to DEHP exposure from use of body lotion only, was found to be close to 100.

Table 2: Calculated MOE for reproductive effects for children based on body lotion use

Infant Age	$D_{int,derm}$ (μg/kg bw/day)	MOE
Newborn	61.7	77
6 months	48.2	99
12 months	42.9	105

The MOEs below and marginally above 100, for young children undergoing critical developmental processes also raise concern for reproductive developmental toxicity from potential DEHP exposure through use of baby lotions and creams.

The use patterns of cosmetic products are likely to vary among individuals and even subpopulations in the general population (e.g. women, men, young adults/teenagers) and the assumptions used in the exposure scenario may lead to overestimation of risk for certain individuals. In addition, the sensitivity of individuals and subpopulations to the critical health effects associated with exposure to DEHP may vary significantly as indicated by the studies in animals demonstrating that developing foetuses and young adults are most sensitive to the DEHP toxicity to reproductive system. Determination of the

level of exposure to DEHP for the different subpopulations that may be at highest risk in the cosmetic use scenario is difficult. However, the results of the large biomonitoring studies where substantial difference was detected between the average levels for the population (mean or median) compared to the level measured for the outliers, clearly indicate that some members of the population have been exposed to much higher DEHP doses than the population average. In particular, a maximum exposure has been calculated for female adults. This raises concerns that the high exposure scenarios with MOE extremely close to or below 100 may be applicable to the subpopulation most at risk for reproductive developmental effects in their progeny i.e. pregnant and breastfeeding women.

Therefore, to ensure that members of the general population are not at risk from repeated exposures to DEHP, it is recommended that DEHP is not intentionally added to cosmetics and personal care products.

Areas of Concern

Considering the current absence of restrictions on DEHP use in cosmetics in Australia and other countries with the exception of the EU and more recently Canada, the potential for introduction of cosmetic products containing DEHP with widespread use and exposure cannot be excluded. Therefore, given the low MOE of 31 and the nature of the reproductive toxicity with a potential for serious long term and irreversible effects especially on the offspring of pregnant and breastfeeding women, potential exposure to DEHP from use in cosmetics is of concern.

Similarly, for young children undergoing critical developmental processes there is a concern for reproductive developmental toxicity from potential DEHP exposure through use of baby lotions and creams based on the MOE estimates which are below or close to 100.

Therefore, it is appropriate to consider amendment to the full form of SUSMP that would prohibit deliberate addition of DEHP to cosmetic and personal care products.

Poisons Schedule Considerations

DEHP is currently not listed in the SUSMP.

Toxicity profile

Acute oral toxicity:	Low: LD50 >5000 mg/kg bw in a rat, mouse, guinea pig, rabbit
Acute dermal toxicity:	Low: LD50 >5000 mg/kg bw in rabbit
Acute inhalation toxicity:	Low; LC50 > 10.62 mg/L in the rat (4h exposure)
Skin irritation:	Minimal in rabbits (in OECD 404 guideline study: no signs of erythema; in study with FDA recommended methods 2/3 very slight erythema. 1/3 well defined erythema-all reversible).
Eye irritation:	Minimal in rabbits (no reaction in cornea or iris in OECD 404 guideline and in FDA recommended methods. Only mild conjuctival redness was observed that was reversible).
.	
Respiratory tract irritation:	no data
Skin sensitisation:	Not a skin sensitiser in guinea pigs
Repeat dose toxicity:	**Liver effect**s in rodents: significant increases in serum albumin, absolute and/or relative liver weights and peroxisome proliferation. NOAEL is 28.9 mg/kg bw/d in 104-week rat dietary study. **Kidneys effects** in rodents: increased absolute and relative kidney weights, mineralization of renal papilla, tubule cell pigmentation and

	chronic progressive nephropathy was observed at higher doses. NOAEL is 28.9 mg/kg bw/d in 104-week rat dietary study. **Testicular effects** in rodents: decreased weights and testicular atrophy, increased bilateral aspermatogenesis, immature or abnormal sperm forms, seminiferous tubular degeneration, Sertoli cell vacuolation or complete loss of spermatogenesis. NOAEL is 3.7 mg/kg bw/d based on an increased incidence of Sertoli cell vacuolation at 37.6 mg/kg bw/d in 13 week dietary study
Carcinogenicity:	**Hepatocarcinogenicity** in rodents regarded as not relevant for humans based on MOA. **Mononuclear cell leukaemia (MCL)** not considered relevant for humans based on species specificity of MLC in the rat test system. **Leydig cell tumours** observed in a single lifetime dietary study with Sprague-Dawley rats and no reliable NOAEL could be determined. However based on postulated MOA the effect is considered relevant for humans.
Genotoxicity:	Predominantly negative results in various systems
Reproductive toxicity:	Toxic effects on fertility and development (mostly of reproductive system) in rodents in both sexes

Critical studies for determination of NOAEL for risk characterisation

Toxicity observed	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	Effect at LOAEL	Species and age at treatment	Reference
Testes/ Fertility	3.7	38	Sertoli cell vacuolation	Rat 4-6 weeks old	Poon et al., (1997)
Testes/ Development	1.2 (m) 5 (f)	5 (m) 15 (f)	↑ testes weight in F1 delay in vaginal opening in F1	Adult rats (F0) and offspring (F1) exposed indirectly through lactation up to PND 21	Andrade (2006) Grande (2006)
Testes/ Fertility	1	10	↑ LH and testosterone levels in serum for group treated PND 21-48	Rats treated at different stages from PND21-62	Akingbemi et al. (2001; 2004)
Fertility/ Development	14	140	↓ number of litters viable per litter in F0	Adult mice (F0)	Lamb et al., (1987)
Fertility/ Development	4.8	14	↓ testes wt, seminiferous tubule atrophy in F1 and F2	Adult rats (F0) and offspring (F1/F2)	Wolfe & Layton (2003)

m-male; f-female

Taken together, noting effects of dose spacing and inherent biological variability, the studies summarized in Table 8.1 support a NOAEL for reproductive toxicity, fertility and developmental

effects, for DEHP in the dose range of 1–10 mg/kg bw/d. Within this range, the most appropriate NOAEL for risk estimates in adults and children is considered to be that determined from the multigenerational study by Wolfe & Layton (2003) of 4.8 mg/kg bw/d.

Other considerations

- Use patterns of cosmetic products are likely to vary among individuals and even subpopulations in the general population (e.g. women, men, young adults/teenagers).
- The sensitivity of individuals and subpopulations to the critical health effects associated with exposure to DEHP may vary significantly as indicated by the studies in animals demonstrating that developing foetuses and young adults are most sensitive to the DEHP toxicity to reproductive system.
- Based on the reproductive toxicity, the undiluted form of DEHP meets the criteria for Schedule 7, particularly the criteria of "a severe hazard from repeated and unprotected use or a significant risk of producing irreversible toxicity, which may involve serious, acute or chronic health risks or even death if it is inhaled, taken internally or penetrates the skin".
- Determination of the level of exposure to DEHP for the different subpopulations that may be at highest risk in the cosmetic use scenario is difficult. Notably, the results of the large biomonitoring studies (Section 5.5 of the PEC report) show that female adults are the subpopulation with maximum exposure levels. This raises concerns that the high exposure scenarios with MOEs extremely close to or below 100 may be applicable to the subpopulation most at risk for reproductive developmental effects in their progeny i.e. pregnant and breastfeeding women. Similarly, for young children undergoing critical developmental processes there is a concern for reproductive developmental toxicity from potential DEHP exposure through use of lotions and creams.
- Use of DEHP in cosmetics and personal care products is prohibited in the EU, Canada and in the State of California in the US. However, there are no restrictions in Asia or other non-EU countries.
- Undiluted DEHP, for occupational purposes, is classified as a reproductive toxicant Category 2 requiring the Risk phrases R60: May impair fertility and R61: May cause harm to the unborn child (http://hsis.ascc.gov.au/SearchHS.aspx) in the Australian Hazardous Substances Information System (HSIS) of Safe Work Australia. The risk phrases above also apply to products containing more than 0.5% DEHP. The impact of listing DEHP in Schedule 7 for uses other than cosmetics may require further consultation. Risks arising from uses other than in cosmetics and toys and childcare articles were not considered in this assessment.
- Currently, in Australia, there is an interim ban under section 65 of the Trade Practices Act 1974 (TPA) on the use of more than 1% DEHP in certain toys and childcare articles. The interim ban remains in force under the new Australian Consumer Law (ACL) provisions that came into effect on 1 January 2011. The current interim ban on children's toys and certain childcare products is in the process of being made a permanent ban under ACL.
- The ban is consistent with the current restrictions on use of DEHP in toys and childcare articles in EU, USA and Canada, although Australia has adopted a higher concentration limit of 1% compared to 0.1% in these countries.

XXXXX

Recommendation for ACCS

The ACCS may consider scheduling DEHP in Appendix C of the SUSMP for intentional use in cosmetics and personal care products to limit the potential for adverse health effects to the Australian public from repeated exposure to DEHP through use of these consumer products.

References:

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NICNAS (2008a) Phthalates hazard compendium: A summary of physicochemical and human health hazard data for 24 *ortho*-phthalate chemicals. National Industrial Chemicals Notification And Assessment Scheme. Accessed from http://www.nicnas.gov.au/Publications/CAR/Other/Phthalate%20Hazard%20Compendium.pdf and http://www.nicnas.gov.au/Publications/CAR/Other/Phthalates.asp

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SCCNFP (Scientific Committee on Cosmetic Products and Non-Food Products) (2003). The SCCNFP's Notes for Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation (5th revision), adopted by the SCCNFP during the 25th plenary meeting of 20 October 2003. The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers, European Commission.

SCCP (Scientific Committee on Cosmetic Products) (2006) The SCCP's Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation 6th Revision. http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_03j.pdf

US FDA (2008) Phthalates and cosmetic products. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Cosmetics and Colors, April 19, 2001; Updated March 31, 2005 and February 7, 2008. Accessed June 2008 at http://www.cfsan.fda.gov/~dms/cos-phth.html

[redacted]

19 January 2011

Comments by [redacted] to the Advisory Committee for Medicines Scheduling – Meeting of 23 February 2011

Proposal

Chloramphenicol – consideration of amending the Schedule 3 entry to restrict chloramphenicol for ophthalmic use only in the treatment of bacterial conjunctivitis.

[redacted] position

[redacted] supports the inclusion of chloramphenicol within Schedule 3 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for *ophthalmic use only* and does not support further restricting the entry *only in the treatment of bacterial conjunctivitis*.

Contact person:

[redacted]

[redacted]

Background

Chloramphenicol is a broad spectrum antibiotic that is active against Gram positive and Gram negative bacteria, rickettsiae and chlamydiae. Infections due to Salmonella typhi, Haemophilus influenzae and Bacteroides fragilis have previously been the principal indications for chloramphenicol use[1]. It is bacteriostatic, preventing bacterial reproduction by selectively inhibiting protein synthesis by bacterial ribosones with a 'reported efficacy of 91% to 93% in ocular infections, and is active against up to 94% of ocular pathogens'[2].

Chloramphenicol is currently included in Schedule 3 (Pharmacist Only Medicines) of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for ophthalmic use only. Products are available as either drop (0.5%) or ointment (1%) formulation, to treat susceptible eye infections.

The two most common brands of chloramphenicol products available in Australia are Chlorsig® and Chloromycetin®. Chlorsig® is registered for use in Australia 'for the treatment of bacterial conjunctivitis and other superficial ocular infections caused by chloramphenicol-sensitive organisms'[2]. Chloromycetin® is registered for use in Australia for 'ocular bacterial infections caused by organisms susceptible to chloramphenicol'[3].

Comments

[redacted] has considered the proposal to amend the Schedule 3 entry for chloramphenicol, and provides the following comments:

1. As per [redacted] to the National Drugs and Poisons Schedule Committee (NDPSC) for meeting 57 (October 2009), [redacted] supports the inclusion of chloramphenicol for ophthalmic use within Schedule 3 of the SUSMP because:

    a. Topical [ocular] chloramphenicol is generally well tolerated, and adverse effects such as hypersensitivity, burning, and stinging sensations are uncommon[4].
    b. Community pharmacy is often the first place that patients with conjunctivitis go for assistance. Pharmacists currently triage patients with conjunctivitis on a regular basis to determine the appropriate course of action.
    c. Pharmacists currently refer patients to the GP where there are complications or where the pharmacist is unsure or concerned
    d. Chloramphenicol is the gold standard against which new antibiotic eye drops are compared and will be effective against nearly all cases of acute bacterial conjunctivitis in adults and children who present in the pharmacy[5].
    e. There are potential savings to both the Medical Benefits Scheme and Pharmaceutical Benefits Scheme.
    f. Patients have quicker and easier access to effective treatment for the treatment of minor bacterial eye infections.
    g. A protocol has been developed by the Pharmaceutical Society of Australia (PSA) for use by pharmacists, a copy of which is included as Attachment A.

[redacted]

With this in mind, [redacted] believes that including *chloramphenicol for ophthalmic use only* within Schedule 3 of the SUSMP continues to meet the scheduling criteria for Schedule 3 medicines provided in the *Scheduling Policy Framework for Medicines and Chemicals*[6].

2. It is now proposed that the Schedule 3 listing for chloramphenicol is further restricted *for ophthalmic use only in the treatment of bacterial conjunctivitis*.

   A consequence of this more restrictive listing would be that chloramphenicol could not be recommended by pharmacists for the treatment of non-complex eye conditions that are not bacterial conjunctivitis, such as blepharitis or styes, even though this would be consistent with the products' registered indications.

   Other items which are included in Schedule 3 of the SUSMP with indications specified (e.g. fluconazole, levonorgestrel, proton pump inhibitors) are consistent with the registered indications for the product.[7] The proposed amendment to the Schedule 3 listing for chloramphenicol is more restrictive than the registered indication for chloramphenicol products. [redacted] is concerned that if this greater restriction is implemented and pharmacists should inadvertently recommend chloramphenicol products for other eye infections for which the product is indicated and registered, they will be breaking the law.

   Without any background information, [redacted] does not support the proposed amendment. We would be interested to know the reasoning for requesting this further restriction. Upon enquiry, the ACMS secretariat advised [redacted] that such information could not be provided. This makes it extremely difficult to determine the most appropriate way to prepare this submission. If there was evidence of public safety issues arising from the current, less restrictive Schedule 3 listing for chloramphenicol, we would reconsider our opposition, but prima facie, we do not support the proposed amendment.

Conclusion

[redacted] supports the inclusion of chloramphenicol within Schedule 3 of the SUSMP *for ophthalmic use only* and does not support further restricting the entry *only in the treatment of bacterial conjunctivitis*.

Reference Sources:

[1] eTG: Therapeutic Guidelines –Antibiotics 2006
[2] ARTG 19662; Chlorsig 1% eye ointment; http://www.tga.gov.au/docs/html/artg.htm
[3] ARTG 56589; Chloromycetin 10mg/g eye ointment; http://www.tga.gov.au/docs/html/artg.htm
[4] Lam RF, Lai JSM, Ng JSK et al; Topical chloramphenicol for eye infections; HKMJ Vol 8 No 1 Feb 2002; 44-47
[5] Marvyn Elton; The Pharmaceutical Journal (Vol 274) 11 June 2005; 725-728
[6] National Coordinating Committee on Therapeutic Goods Scheduling Policy Framework for Medicines and Chemicals – 1 July 2010; www.tga.gov.au
[7] Postinor-1(levonorgestrel) – ARTG 149269; Diflucan One (fluconazole) – ARTG 100596; Proton Pump Inhibitors e.g. Somac Heartburn Relief (pantoprazole) – ARTG 154252

[redacted]

ATTACHMENT A:

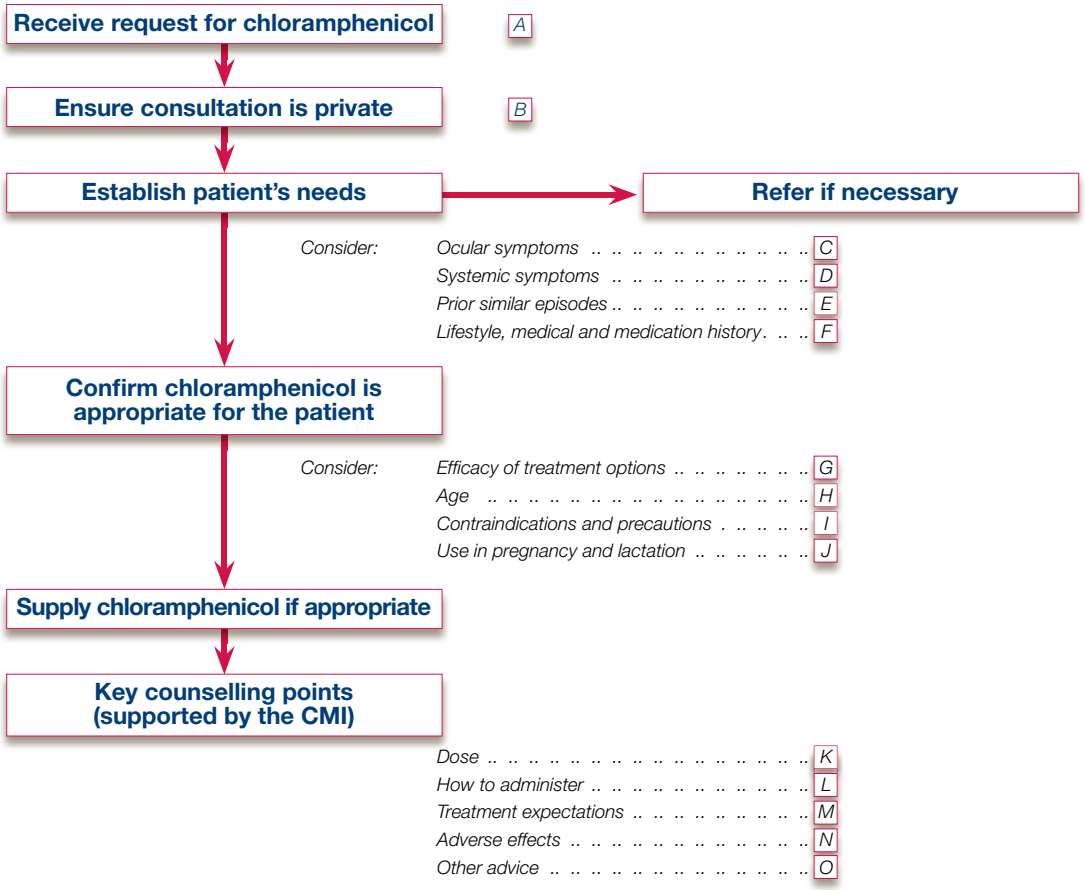
PSA Protocol – Provision of chloramphenicol for ophthalmic use as a *Pharmacist Only Medicine*

[redacted]

Pharmaceutical Society of Australia

Provision of chloramphenicol for ophthalmic use as a *Pharmacist Only* medicine

May 2010



Explanatory notes

Pharmacists are expected to exercise professional judgment in adapting the guidance provided to specific presenting circumstances.

A. Professional Standards

The professional standards[1] outline the appropriate actions to be taken by pharmacists and trained pharmacy staff in response to a direct product or symptom-based request.

B. Privacy

Pharmacists must meet their obligations in relation to respecting the patient's privacy and confidentiality in the provision of *Pharmacist Only* medicines and associated patient counselling.[2]

C. Ocular symptoms[3]

Bacterial conjunctivitis is typically characterised by:

- Discharge that may be sticky and mucopurulent. Patients may find it difficult to open their eyes in the morning, due to dried crust. The discharge may cause some blurring, particularly upon waking.
- Red or pink conjunctiva (the transparent surface that covers the white of the eye and the inside of the eyelid).
- A burning or gritty sensation in the eye.

It usually starts in one eye and then spreads to the other.

Other common conditions can produce similar ocular symptoms; however:

- Viral conjunctivitis is associated with a more watery discharge.
- Allergic conjunctivitis is associated with a watery discharge and itching.

It is essential to exclude serious causes of a red eye that can lead to permanent impairment of vision.

Referral to an optometrist or general practitioner is required in the presence of any of the following:

- Photophobia
- Severe pain in the eye or pain and swelling around the eye
- Loss of, reduced or blurred vision
- Restriction of eye movement

- Cloudy cornea
- Copious yellow-green purulent discharge that accumulates after being wiped away
- Contact lens wear
- Pupils that look abnormal, i.e. irregular, torn, dilated or not reactive to light
- Injury to the eye or suspicion of a foreign body in the eye
- A history of welding without eye protection immediately prior to onset of symptoms.

D. Systemic symptoms[3]

Bacterial conjunctivitis does not typically present with any systemic symptoms.

Systemic symptoms may assist in differentiating bacterial conjunctivitis from other common conditions that can produce similar ocular symptoms:

- Viral conjunctivitis is often associated with an upper respiratory tract infection.
- Allergic conjunctivitis is often associated with symptoms of hayfever or allergic rhinitis.

Referral to an optometrist or general practitioner is required if:

- The patient feels unwell.

E. Prior similar episodes

Referral to an optometrist or general practitioner is required if the patient has had similar symptoms in the past few weeks.

F. Lifestyle, medical and medication history

Referral to an optometrist or general practitioner is required if the patient:[3,4]

- Has glaucoma or dry eye syndrome
- Is using other eye drops or eye ointments at the time of presentation
- Is a contact lens user (as they have a greater risk of serious eye infection by *Pseudomonas aeruginosa*, which is not susceptible to chloramphenicol and may require hospital admission)
- Has had eye surgery or laser treatment in the past six months
- Has a history of bone marrow problems – individual or family (local application of chloramphenicol has been associated with rare cases of bone marrow hypoplasia, including aplastic anaemia and death)
- Has recently travelled overseas.

G. Efficacy of treatment options

The majority of acute bacterial conjunctivitis cases spontaneously resolve within five days.

There are generally no complications if left untreated. The purpose of treatment is to speed resolution and reduce the likelihood of transmission.

All cases of bacterial conjunctivitis may be treated with chloramphenicol ophthalmic preparations provided there is no reason to refer the patient.[3] However, in mild cases, it may be sufficient to use propamidine 0.1% eye drops.[5]

H. Age

Bacterial conjunctivitis has a higher incidence in children and the elderly.[3]

Chloramphenicol ophthalmic preparations can be used in children of any age.[6,7] However, pharmacists should consider that in infants, the eyes are developing and it is difficult to exclude serious causes of a red eye that can lead to permanent impairment of vision without ocular examination.

Referral to an optometrist or general practitioner would be appropriate for children <2 years.[3]

I. Contraindications and precautions

Ophthalmic chloramphenicol is contraindicated in patients with a history of hypersensitivity and/or toxic reaction to chloramphenicol or to any other ingredient in the drops or ointment base, and in patients with a family history of blood dyscrasias.[4]

J. Use in pregnancy and lactation

Ophthalmic chloramphenicol is classed category A by the Australian Drug Evaluation Committee.[4]

Although the use of systemic chloramphenicol by the mother may cause serious toxicity in the infant or fetus, topical chloramphenicol in the recommended dose is safe to use during pregnancy, and single courses of eye drops are considered safe in breastfeeding.[4,8]

K. Dose

For bacterial conjunctivitis use chloramphenicol 0.5% eye drops, one or two drops every two hours initially, decreasing to six-hourly as the infection improves. Chloramphenicol 1% eye ointment may be used at bedtime.[5]

Alternatively the eye ointment may be applied every three hours.[4]

Treatment should continue for at least two days after the eye appears normal.[3,4]

L. How to administer

Conjunctivitis is contagious. Before and after application, hands should be washed and dried. To administer eye drops or ointment, the head should be tilted back and the lower eyelid gently pulled out to form a pouch.

For drops, the bottle should be squeezed to release one drop into the lower eyelid. Do not touch the eyelids or lashes. See APF21[9] for more detailed instructions. This process should be repeated for application of each drop, and for the other eye, if both eyes are infected.

For ointment, 1.5 cm should be applied into the lower eyelid.

M. Treatment expectations

Symptoms should improve within 48 hours of commencing treatment. Patients should be advised to consult an optometrist or general practitioner if symptoms do not improve within this timeframe or become worse. These may indicate infection by non-susceptible organisms.[3] The development of alarm symptoms (e.g. pain, loss of vision, photophobia) is likely to require urgent referral to an ophthalmologist.

N. Adverse effects

Adverse effects are usually minor and may include a transient stinging sensation in the eye when applying the drops. Local allergic reactions manifest as eye redness and swelling. Transient blurring of vision may occur, and patients should be advised not to drive or operate machinery unless their vision is clear.[3]

Serious adverse effects include hypersensitivity reactions that may manifest as angioneurotic oedema, fever, anaphylaxis and vesicular and maculopapular dermatitis. Superinfection with candida may also occur. Treatment should be immediately discontinued in such cases.[3]

O. Other advice

Prior to opening, the drops should be stored in the fridge (2–8°C). After opening, the drops and ointment can be stored below 25°C for up to one month and should then be discarded.[4]

Provision of a CMI leaflet and *Red and dry eyes* Self Care Fact Card or other printed information for consumers is appropriate.

References

1. Pharmaceutical Society of Australia. Standards for the provision of Pharmacy Medicines and Pharmacist only medicines in community pharmacy. In: Professional Practice Standards (version 3). Canberra: PSA, 2006.
2. Guidelines for pharmacists. Professional practice and the Privacy Act. Canberra: PSA, 2001.
3. Royal Pharmaceutical Society of Great Britain. Practice Guidance: OTC chloramphenicol eye drops. June 2005.
4. eMIMs December 2009.
5. eTG complete [CD-ROM]. Melbourne: Therapeutic Guidelines Limited; 2009 Nov.
6. British National Formulary for children. 2009 .Accessed online 8/4/10.
7. Paediatric Handbook, 8th ed. Melbourne: Royal Children's Hospital, 2009.
8. Drugs and Breastfeeding. Melbourne: Royal Women's Hospital, 2006.
9. Sansom LN, ed. Australian Pharmaceutical Formulary and Handbook, 21st edn. Canberra: PSA, 2009.

JN2732

2.1.2 Fexofenadine - submission 1/6

21 December 2010

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601
Via email: SMP@health.gov.au

Dear the Secretary,

RE: Fexofenadine Rescheduling Application

I write regarding the supplementary invitation for public comment by the Advisory Committee on Medicines Scheduling as published on the TGA website on 16 December 2010.

As a leading provider of health and wellness products to consumers, XXXXX actively supports the application: *Fexofenadine – proposal to amend the current Schedule 2 fexofenadine entry to exempt oral fexofenadine for the short-term symptomatic relief of seasonal allergic rhinitis from the requirements of scheduling*.

This consideration may include limiting the exemption to:

- small pack sizes (10 dosage units or less);
- packs containing not more than 5 days' supply at the maximum dose recommended on the label;
- for the treatment of adults and children aged 12 years of age and over; and
- a maximum daily dose of 120 mg.

With XXXXX we believe that the consumer benefits of increasing access to allergy treatments are significant.

The grocery industry has demonstrated benefit through the extended availability of treatments including but not limited to:

- Cold & flu
- Nicotine replacement
- Heartburn relief
- Pain relief.

These treatments continue to be sold in both pharmacy and grocery channels and we believe that improved access to these treatments for consumers has led to faster initiation of treatment.

In the case of Fexofenadine Hydrochloride we believe that increasing access to small, low dose packs of this treatment will allow consumers to better manage their seasonal allergic rhinitis and we are confident in the ability of the grocery sector to manage the distribution of the product appropriately.

Should you have any questions relating to our submission please feel free to contact XXXXX

Yours sincerely

XXXXX

2.1.2 Fexofenadine - submission 2/6

[redacted]

21/12/2010 02:36 PM

[redacted]

To <SMP@health.gov.au>
cc
bcc
Subject RE: [redacted] Down?scheduling ? Invitation for public comment to TGA/A
[SEC=UNCLASSIFIED]

DOCUMENT NOT YET CLASSIFIED

Dear [redacted]

Please consider my email (following) to be a pre-meeting comment in relation to this proposal. Thank you.

'To Whom It May Concern

We know with hayfever, in particular, getting a good night's sleep can be extremely hard. Resulting fatigue can severely affect a sufferer's ability to function the next day – for instance driving safely, being productive and attentive within the work place, having the ability to concentrate while studying or remaining vigilante when taking care of children.

As with all allergies it is critical to keep hayfever under control and stay on top of symptoms. This means ensuring sufferers can access treatment as and when their condition is triggered or when they experience a 'flare-up'. Being able to find treatment easily and when needed on a supermarket shelf – such as when trying to get to sleep at night or when symptoms start suddenly before getting to work - will be an important step in helping sufferers maintain control.

Like all allergy sufferers, people with hayfever are extremely familiar with their symptoms, they have a very good understanding of their condition and are completely capable of self-treatment. They will generally treat themselves during the hayfever season having minimal interaction with a pharmacist.

[redacted] has been around now for a very long time. It is a well-known and effective treatment for hayfever. It is also a treatment – which from my understanding is significantly safer to use than many of the common grocery medications currently available – namely paracetamol and ibuprofen.

This de-scheduling approval will give thousands of sufferers the ability to manage their hayfever more effectively during the hayfever season and be a safe and productive member of the workforce and community.

We urge you to make a positive recommendation to approve this application.'

Kind Regards

[redacted]

[redacted]

2.1.2 Fexofenadine - submission 3/6

[redacted]
29/12/2010 07:21 AM

To "SMP@health.gov.au" <SMP@health.gov.au>
[redacted]
bcc
Subject RE: [redacted] Down-scheduling - Invitation for public comment to TGA/ACMS

For Follow Up: Low Priority

DOCUMENT NOT YET CLASSIFIED

Manager,
Scheduling Secretariat
GPO Box 9848 CANBERRA ACT 2601

re Call for Public Comment concerning potential [redacted] Down-scheduling

I have been advised by [redacted] that there has been a call for Public Comment on the potential down-scheduling of [redacted] (fexfenadine hydrochloride) for access through grocery channels. I made a submission to the MSEAC dated April 28th, 2010 which I paraphase again to contribute to the debate concerning this matter.

I write in my capacity [redacted]

I acknowledge that [redacted] requested an independent, expert opinion in relation to the TGA response to an application for a change regarding the current access arrangements for fexofenadine.

Disclosure

I was engaged by [redacted] for my expert opinion for which I have been reimbursed.

Conflict of Interests

The opinions expressed are my own and do not reflect those of [redacted]

Issue

[redacted] is applying [redacted] to the Advisory Committee on Medicines Scheduling to make low dose fexofenadine [redacted] tablets available through grocery channels. The drug would be available in small packs (enough for a maximum of 5 days treatment, 10 units per pack, maximum daily dose 120mg) for the treatment of SAR (Seasonal Allergic Rhinitis) in adults. The drug is in Schedule 2,that is, available in 'front of the counter' in pharmacy.

Previous Evaluation recommending rejection

I have had the opportunity to review the Conclusions and Evaluator's Recommendation associated with the application dealt with in June 2009.

The evaluator noted that "SAR is common and burdensome" and the fexofenadine "is a safe and effective treatment option". However, there were two concerns. The first was that without pharmacist input to the process misdiagnosis rates would be too high. Secondly the safety in pregnancy and lactation is 'unknown', the present category being B2 for pregnancy and designated not recommended for breast-feeding mothers. Finally, the case for this expanded access was not convincingly made in the view of the evaluator.

Commentary on Concerns

Fexofenadine is the active metabolite of terfenadine. It is an orally-active and non-sedating histamine H1-receptor antagonist available as [redacted] in Australia since 1996. It is scheduled S2 (in front of the counter in pharmacies) at present.

In order to promote the safe and effective use of OTC medications the quality of the labelling on the product packaging is critical. Directions for use and warnings against using the drug in pregnancy and during breast-feeding have been highlighted clearly and more explicitly in anticipation of access to the medicine through grocery channels in limited amounts. I note *inter alia,* that medicines with more concerning pregnancy warnings are available through grocery channels e.g. aspirin and ibuprofen (Pregnancy Category C respectively).

Fexofenadine is well tolerated in the doses recommended and the long experience with the medicine has allowed its availability under Schedule 2 in pharmacy. Nuisance side effects in very small numbers of patients are noted in the PI and these have not been distinguishable in number from placebo treatment in controlled trials. Reactions include symptoms involving the GI tract (nausea), CNS (headache, drowsiness, dizziness), and skin (rashes, pruritis, angioedema). Rarely cases of anaphylaxis, chest tightness and dyspnoea have occurred.

No new data has emerged regarding potential hazards of this drug in pregnancy and to the foetus. The category B2 indicates that the drug has been taken by only a limited number of pregnant women, without an increase in the frequency of malformations or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals show no evidence of an increased occurrence of foetal damage. There is a clear warning against the use of the drug in pregnancy on the packaging and in the Consumer Medicines Information available with the medicine.

Similarly, there is a warning on the packaging against taking the medicine when breast-feeding. There are no new data in addition to that found in the Product Information. A study in the leading clinical pharmacology journal, Clinical Pharmacology and Therapeutics (Lucas et al, 1995) examined the pharmacokinetics (PK) of the drug in lactation and was reassuring as to the small quantities a baby could consume if the breast-feeding mother consumed terfenadine (pro drug for fexofenadine) according to the instructions on the package. Lucas et al conclude: " **Newborn dosage estimates based on the highest measured concentration of terfenadine**

metabolite *(fexofenadine-my inclusion)* in milk suggests the maximum level of newborn exposure would not exceed 0.45% of the recommended maternal weight-corrected dose. Estimated amounts consumed by the neonate after the mother is given the recommended dose of the drug are not likely to result in plasma levels producing untoward effects."

The argument for access through grocery channels for limited supply of fexofenadine rests on the significant and distressing symptoms associated with SAR such as nasal congestion, sneezing, itching and sore eyes (Plaut & Valentine, 2005; Walls et al, 2005), the often acute onset of these experienced outside normal business hours, the associated decrement in quality of life and notably, the interference with sleep. Timely use of H1 antihistaminic such as fexofenadine is a proven safe and effective option amongst a number of options. Advice about the medicine and how to use it safely is readily available on the packaging and this has been upgraded in order to be clearer and more explicit. Advice also to consult a pharmacist should resolution of symptoms be unsatisfactory or untoward effects are suspected is also an important communication transmitted to the consumer by way of the packaging.

Given the long history of safe and effective use as an S2 medicine in Australia, the upgrading of information on the packaging, the proposed limited quantities available through grocery channels and the benefits of timely and easier access to the medicine when SAR symptoms occur 'out of hours' especially, are the reasons that I feel the change in access proposed is reasonable and will be helpful to many.

References

Lucas BD, Purdy CY, Scarim SK. Terfenadine pharmacokinetics in breast milk in lactating women.Clin Pharmacol Ther. 1995; 57(4):398-402.

Plaut M, Valentine MD. **Allergic Rhinitis** N Engl J Med 2005; 353:1934, *Clinical Practice*

Walls RS, Heddle RJ, Tang MLK, Optimising the management of allergic rhinitis: an Australian perspective Med J Aust 2005; 182 (1):28-33

Yours Sincerely,

[redacted]

DOCUMENT NOT YET CLASSIFIED

2.1.2 Fexofenadine - submission 4/6 4/6

[redacted]

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Dear Sir,

Re: Public Submission – under Reg. 42ZCZK of the Therapeutic Goods Regulations 1990. 22nd February Meeting of the ACMS.

We refer to the pre-February 2011 Scheduling Meeting notice and wish to comment specifically on the application to reschedule fexofenadine for oral use for the short-term treatment of seasonal allergic rhinitis in pack sizes of not more than 10 dosage units. The comments below address a matter mentioned in section 52E of the Therapeutic Goods Act.

[redacted] believes that the existing scheduling should continue to apply for fexofenadine.

Fexofenadine is one of a class of second generation antihistamines. As such these products are sold in pharmacies where advice is readily available. Although consumers may self-select these products, they also have the opportunity to ask questions if they are taking other medicines and to ask about adverse events they may already have experienced with a particular medicine. This advice is not readily available with unscheduled products and some new users would be attracted to the smaller packs in grocery to "try" the medicine if they have symptoms suggestive of seasonal allergic rhinitis. Repeat purchasers may perhaps be more likely to buy the larger pharmacy-only packs.

In situations where new users of the drug could potentially be self-selecting, a pharmacist's or pharmacy assistant's advice may be necessary. The symptoms of seasonal allergic rhinitis can often be confused with other conditions, such as common cold and chronic rhinitis or non-allergic rhinitis. In these situations, a pharmacist's advice is necessary to aid correct diagnosis. Other situations such as pregnancy, breastfeeding, and use with antacids may also require a pharmacist's advice.

Since fexofenadine is one in a range of second generation antihistamines, sponsors of other second generation antihistamine products will, in a similar way, apply to exempt their product from the scheduling should exemption be granted for fexofenadine.

Should the ACMS exempt fexofenadine, some consumers may interpret the presence of fexofenadine in the grocery setting as an indication that this product is "safer" than its pharmacy only competitors. When considering scheduling, it is important for the ACMS to consider the "landscape" of the different products within the same class, not only the individual medicine, so that consumers do not have a misleading impression of the safety of one product over the others.

[redacted]

Fexofenadine does not carry a drowsiness warning in Australia and is not listed in Appendix K. In New Zealand, however, all second generation antihistamines are required to carry the following label warning (see Reg 22 of the Medicines Regulations 1984):

"Although the medicine is unlikely to affect your ability to drive or operate machinery, a few people may be impaired and care should be taken."

We believe that this is a suitable approach in that it is class-wide, and it accurately assesses the low risk of these adverse events but nonetheless advises people to be cautious. Even if a few people are affected by these particular effects, it is advisable to inform all people of the risk, particularly if supply is further de-regulated and people rely only on the product label and the company's promotional material for information about whether the drug is suitable for them. Other label warnings should be consistent across the range.

We believe that this is a suitable approach in that it is class-wide, and it accurately assesses the low risk of these adverse events but nonetheless advises people to be cautious. Even if a few people are affected by these particular effects, it is advisable to inform all people of the risk, particularly when supply is further de-regulated and people rely only on the product label and the company's promotions for information about whether the drug is suitable for them.

Please contact me if you have any further queries regarding the above.

Yours sincerely,

2.1.2 Fexofenadine - submission 5/6

[redacted]

21 December 2010

The Secretary
Scheduling Secretariat
Advisory Committee on Medicines Scheduling
GPO Box 9848
CANBERRA ACT 2601

To the Secretary

As a pharmacist with more than [redacted] of experience in the Australian pharmacy space, I am writing to express my support for the proposed down scheduling of Fexofenadine (Telfast).

[redacted]

I understand that [redacted] has made a submission to the Advisory Committee on Medicines Scheduling (ACMS) to approve the down scheduling of emergency presentations of Fexofenadine from pharmacy-only to the grocery market.

My understanding and experience with Fexofenadine is that it is the active metabolite of terfenadine. It is an orally-active and non-sedating histamine H1-receptor antagonist available as Telfast in Australia since 1996. It is scheduled S2 (in front of the counter in pharmacies) at present.

The safety of Fexofenadine has been demonstrated extensively in both toxicological studies and clinical trials. Additionally, there is a long and established history of safe and effective use of Fexofenadine for treatment of seasonal allergic rhinitis (SAR) in Australia and internationally.

While some subsets (eg, pregnant and breastfeeding women) of the population should not take it unless advised to do so by their Doctor or Pharmacist, Fexofenadine is generally well tolerated among the majority of sufferers of hay fever.

[redacted]

[redacted]

Sufferers of SAR experience distressing symptoms such as nasal congestion, sneezing, itching and sore eyes, which can impact quality of life, productivity and interfere with sleep. The acute onset of these symptoms often occurs outside normal business hours, which is why access to treatment through grocery stores (many of which offer access to consumers on either a 24 hour basis, or similarly long hours, eg 6.00am – 10.00pm) is necessary.

Timely use of H1 antihistaminic such as Fexofenadine is a proven safe and effective treatment amongst a number of treatment options. Advice about the medicine and how to use it safely is readily available on the packaging and I am advised that this has been upgraded in order to be clearer and more explicit.

I would like to reiterate that advice to consult a pharmacist should resolution of symptoms be unsatisfactory or untoward effects are suspected, is also an important communication transmitted to the consumer by way of the packaging.

Importantly, while both the grocery and pharmacy models provide options to consumers to manage health conditions, in a number of instances, both groups share the responsibility for patient management. For many years now, the Australian grocery sector has played an important role in assisting Australian consumers to effectively manage a variety of conditions such as headaches, general pain, coughs and colds, heartburn and smoking cessation.

This is demonstrated through access to lower dose, or small emergency size options in grocery, and full dose and larger pack options in the pharmacy. An excellent example of this is *Nurofen* (200mg ibuprofen in pack sizes of 6, 12, 24) – available in grocery; and *Nurofen Plus* (12.8mg of codeine and 200mg of ibuprofen in pack sizes of 12, 24 and 48) – pharmacy only. It is also noteworthy that some of these products had a higher pregnancy safety classification than Fexofenadine.

Therapeutic options available that have undergone down scheduling to allow grocery access to consumers for the management of these conditions include:

Nicotine
- Nicabate

Ibuprofen
- Nurofen, Advil, Herron Blue Ibuprofen, Coles Tablets Ibuprofen, Homebrand Ibuprofen

Aspirin
- Aspro Clear, Disprin, Coles Tablets Aspirin, Homebrand Aspirin

Phenylephrine
- Panadol Cold & Flu + Decongestant
- Nyal Cold & Flu Medicine, Nyal Nasal Decongestant PE, Nyal Nasal Decongestant + Pain Relief PE Tablets, Nyal Sinus + Pain Relief PE, Nyal Sinus Relief Elixir

Ranitidine
- Mylanta Ranitidine
- Zantac

I also note that New Zealand currently approves provision of small emergency packs of Fexofenadine in grocery stores. The United Kingdom has also down scheduled specific antihistamines which are now available for general sale.

[redacted]

[redacted]

Given the long history of safe and effective use in Australia, the OTC experience of antihistamines in the UK and New Zealand, the upgrading of information on the packaging, the proposed limited quantities available through grocery and the benefits of timely and easier access to the medicine when symptoms occur 'out of hours', I believe the proposed change in access for Fexofenadine is reasonable and will be of benefit for many patients.

Sincerely

[redacted]

[redacted]

[redacted]

19 January 2011

Comments by [redacted] to the Advisory Committee for Medicines Scheduling

– Meeting of 23 February 2011

Proposal

Fexofenadine – proposal to amend the current Schedule 2 fexofenadine entry to exempt oral fexofenadine for the short-term symptomatic relief of seasonal allergic rhinitis from the requirements of scheduling.

[redacted] recommends that fexofenadine in preparations for oral use for the short term symptomatic relief of seasonal allergic rhinitis remain listed under Schedule 2 of the Standards for the Uniform Scheduling of Medicines and Poisons (SUSMP).

Contact person:

[redacted]

[redacted]

Background

Allergic rhinitis is an inflammatory disorder of the nose induced by allergen exposure of the mucous membranes lining the nose, characterised by rhinorrhoea, itching, sneezing and nasal obstruction. Traditionally, allergic rhinitis has been classified into three subgroups – seasonal, perennial and occupational. The World Health Organisation's (WHO) Allergic Rhinitis and its Impact on Asthma (ARIA) group has revised the classification to take into consideration the severity of the disease and its impact on a patient's quality of life. The revised classification includes 'intermittent' for episodes lasting less than one month or four days a week, and 'persistent' for episodes lasting more than one month or more than four days a week.[1]

Histamines are the major mediator of the early phase reaction for allergic rhinitis. A late phase reaction occurs a few hours after allergen exposure and is associated with cellular eosinophilic inflammation of the nasal mucosa and expression of endothelial and epithelial adhesion molecules, chemokines and cytokines.[1] Antihistamines are commonly used as a first-line treatment – they are particularly effective at relieving symptoms, such as sneezing, itching and watery rhinorrhoea. Second-generation antihistamines have a higher potency and longer duration of action compared with the first-generation sedating antihistamines.[1]

Fexofenadine, a metabolite of terfenadine, is a non-sedating, second-generation antihistamine mainly used for the treatment of seasonal allergic rhinitis (SAR) in adults and children over 6 years. It is available as 30mg, 60mg, 120mg and 180mg tablets under Schedule 2 of the SUSMP. The 60mg, 120mg and 180mg tablets are designed for adults and children 12 years and over, at doses of up to 180mg per day. The 30mg tablets are for children 6 to 11 years at a dose of one tablet twice daily when required. Safety and effectiveness in children below the age of 6 years has not been established.

At the June and October meetings of 2009, the National Drugs and Poisons Schedule Committee (NDPSC) considered a submission proposing an exemption for fexofenadine from scheduling for the short-term treatment of SAR. Following a decision in November 2009 by New Zealand's Medicines Classification Committee (MCC) to exempt fexofenadine from scheduling for a maximum of five days therapy and daily dose of up to 120mg, the matter was referred again to the NDPSC in February 2010 to reconsider exempting fexofenadine from scheduling in Australia. On all occasions to date, the NDPSC has determined that including fexofenadine within Schedule 2 of the SUSMP remained appropriate.

Comments

[redacted] has considered the proposal to exempt oral fexofenadine for the short-term symptomatic relief of SAR from the requirements of scheduling and provides the following comments with consideration given to the scheduling factors provided in the *Scheduling Policy Framework for Medicines and Chemicals*[2] (Scheduling Framework).

1. In considering the appropriate schedule category for a medicine, and whether medicines should be exempt from scheduling in specific instances, consideration must be given to the nature of the condition to be treated as well as the use, abuse and safety profile of the medicine.

[redacted]

1.1. It is interesting to note that in its July 2009 submission to New Zealand's MCC when applying for a reclassification of fexofenadine[3], [redacted] claims that 'SAR can be easily self-diagnosed' and is 'unlikely to mask a more serious underlying disease.' It also states that there is 'a wide range of over-the-counter treatments for SAR', that 'most adult sufferers self medicate for SAR and 'nearly two-thirds of respondents did not consult their doctor about their current SAR treatment'. The submission does not however acknowledge that the treatments for SAR have been available through community pharmacies where patients have been supported by professional pharmacist advice when needed.

Although second-generation antihistamines such as fexofenadine have a relatively good safety profile and are not likely to be abused or misused, SAR is not a benign condition that should be left to patient self-diagnosis or self-management. There are potentially serious consequences that can result from the incorrect diagnosis or improper management of SAR and [redacted] believes that Schedule 2 of the SUSMP is the appropriate schedule for listing these antihistamines as it facilitates access to advice from a health care professional.

National Asthma Council Guidelines[4]report that 20-30% of patients with known allergic rhinitis also have asthma and that patients can mistake symptoms of allergic rhinitis for asthma. A 2006 European paper[1] reports that 40-50% of patients with allergic rhinitis suffer from asthma and more than 90% of asthmatics also have rhinitis. It also identifies that chronic nasal congestion may result in rhinosinusitis and the obstruction of sinus ostia due to infections predisposed by negative pressure and mucous stagnation and that nasal polypsis may result from the chronic inflammation of nasal mucosa.

In addition, severe SAR episodes warrant health care professional intervention as patients may experience sleep disturbance, impairment of daily activities or participation in leisure or sporting activities as well as impairment of school or work activities.[5]

1.2. WHO's ARIA details the importance of pharmacists in identifying symptoms of allergic rhinitis and recommending appropriate treatments[6]. It highlights the role pharmacists can play in:

- recognising allergic rhinitis and assessing its severity
- understanding the effect of treatment on rhinitis and co-morbidities
- determining whether management in the pharmacy is appropriate
- initiating an appropriate treatment and monitoring plan and
- proposing appropriate preventive measures.

With Schedule 2 medicines, pharmacy assistants are taught how to triage patients and when to refer to the pharmacist. As part of the Quality Care Pharmacy Program (QCPP), it has been a requirement since 1 March 2008 that pharmacy personnel who assist the pharmacist with the supply of Schedule 2 or Schedule 3 medicines must have completed the relevant training relating to the supply of *Pharmacy Medicines* (Schedule 2) and *Pharmacist Only Medicines* (Schedule 3).

Should fexofenadine be exempted from scheduling, patient's could access this medicine from a variety of retailers other than pharmacy, including supermarkets

[redacted]

and service stations. There is no support available to assist the patient or to intervene should the patient be selecting multiple packs of fexofenadine or purchasing it in combination with other products which, in a pharmacy, would likely prompt referral to the pharmacist (e.g. decongestant nasal spray, decongestant tablets, lozenges).

1.3. Pharmacists are trained to triage and assess patients with rhinitis symptoms and to recommend the safest and most appropriate course of action. When a medicine is indicated, there may be times when it is more appropriate to use a nasal corticosteroid spray, or an antihistamine/decongestant combination. Pharmacists also know to refer patients to their general practitioner (GP) if symptoms are severe, recurring frequently, are perennial or non-responsive to treatment. When considering the most effective treatment for SAR, it is important to consider the symptoms in order to make an appropriate diagnosis. Other conditions with similar symptoms include viral or bacterial rhinosinusitis, chronic rhinitis, rhinitis medicamentosa, non-allergic rhinitis and foreign bodies in the upper airway.

Intranasal corticosteroids are more effective than antihistamines in controlling symptoms of allergic rhinitis as well as non-allergic rhinitis.[4] Treatment of allergic rhinitis with intranasal corticosteroids reduces the risk of asthma-related emergency department visits and hospitalisation in patients with asthma and co-existing allergic rhinitis and may improve lung function.[4] With this in mind, it is important that people with SAR who may have undiagnosed or uncontrolled asthma to have access to health care professional advice to assess the symptoms and recommend the most appropriate course of action.

We note that the Sanofi Aventis submission to the MCC[3] reported that 'the prevalence of allergic rhinitis represents a significant economic burden'. Facilitating pharmacist intervention is a safety check mechanism that can alleviate this economic burden. If patients with more severe forms of SAR or with other co-morbidities such as uncontrolled or undiagnosed asthma were to self-diagnose and self-treat their condition without any access to health care professional intervention, there could be an even greater adverse impact on the economy. Patients should have access to advice from a health care professional about the most appropriate course of action for their condition, and if this involves the recommendation of a medicine, then it should be for the most appropriate and effective treatment for them.

[redacted] has had anecdotal reports from members that the 2010 hay fever season has been particularly bad, and that many patients have been reporting that their usual second-generation antihistamine treatment has not been as effective, and that alternative or additional therapies have been required. Some patients have reported increasing their antihistamine dose of their own accord because the antihistamines have not been working.

From the public perspective, it is more cost-effective to have free and easily accessible professional advice from a community pharmacist based on the symptoms presented and medicine history, than to select products off a supermarket shelf for trial and error. If patients have been increasing their antihistamine dosage because of lack of efficacy or finding their usual treatment

[redacted]

ineffective, pharmacists are able to assess and make appropriate recommendations, which may include transferring to or augmenting with another medicine or referring the patient to their GP.

2. In determining whether a medicine should be exempted from scheduling, the Committee has the responsibility to balance the protection of all elements of the public against any demonstrated need for increased access.

   2.1. Reiterating the concerns expressed in previous submissions from [redacted] for this matter, fexofenadine is classified as category B2 for pregnant women[7], meaning human data is lacking or inadequate. The primary concern of [redacted] remains and relates to the safe use of this product in at-risk population groups due to increased availability.

   It is not appropriate to rely solely on label warnings to caution against the use of fexofenadine in pregnancy as it has been recognised that the public's general poor health literacy is a significant issue and people do not always read and follow the directions or warnings contained on or within the packet. From a range of 5 levels for health literacy, when examined by age, only 48% of females aged 15-44 years achieved health literacy of Level 3 or above[8].

   2.2. [redacted] also questions any argument for an increased need for access to treatments for SAR. A quick perusal of the Canberra yellow pages shows that there is at least one pharmacy open from 9am to 11pm every day of the year. There are some pharmacies open until 9pm and 10pm and even more open until 6pm, 7pm and 8pm. Many of the listed pharmacies are open seven days so urgent treatment could be accessed within a nine to fourteen hour period if needed. One would assume that other capitals and major metropolitan areas would have similar pharmacy services and many country towns now have access to pharmacy services every day of the week. In addition, states and territories have special licensing arrangements in place for Schedule 2 medicines to be available in areas without access to a pharmacy.

   There are also several brands of fexofenadine on the market (Allerfexo®, Amcal Fexo®, Chemist Own Fexo®, Fexal®, Fexotabs®, Guardian Fexo®, Tefodine®, Telfast®, Xergic®)[9] as well as other second-generation antihistamines such as loratadine and cetirizine. With such extensive competition within the pharmacy sector, there is not a strong argument that increasing access from other sectors would significantly reduce the retail price of these products as this is already the case.

[redacted] maintains that people with SAR already have extensive access to cost-effective treatments through the community pharmacy network and that any benefit of increasing access would not outweigh the risks. In addition, retaining the Schedule 2 listing for second-generation antihistamines ensures people with SAR have access to the expertise and advice of a highly trained health care professional.

[redacted]

Conclusion

Patients currently have access to fexofenadine through the 5000 plus community pharmacies throughout Australia, many with extended trading hours, with the opportunity to access pharmacist assessment, counselling and advice. The safety profile of fexofenadine is not the only issue. Considering the significant risk of other co-morbidities associated with SAR, particularly uncontrolled or undiagnosed asthma, as well as the B2 pregnancy risk category and the fact that there is no demonstrated need for increased access to SAR treatments, [redacted] does not believe it is appropriate for fexofenadine to be exempted from scheduling and that such a decision would be to the detriment of public safety and the quality use of medicines.

Overall, [redacted] recommends that fexofenadine, in preparations for oral use for the short-term symptomatic treatment of SAR, remains under Schedule 2 of the SUSMP.

Reference Sources:

[1]Geirgio W Canonica and Enrico Compalati; Allergic Rhinitis; Business Briefing – European Pharmacotherapy; 2006

[2] National Coordinating Committee on Therapeutic Goods Scheduling Policy Framework for Medicines and Chemicals – 1 July 2010; www.tga.gov.au

[3] Sanofi Aventis Submission to the Medicines Classification Committee for: Reclassification of Fexofenadine; 28 July 2009; http://www.medsafe.govt.nz/profs/class/mcc42Telfast.pdf

[4] A guide for health professionals: Allergic rhinitis and the patient with asthma; September 2006; National Asthma Council; www.nationalasthma.org.au

[5] Therapeutic Guidelines – Respiratory 2009; eTG; http://online.tg.org.au/complete/

[6] WHO Allergic rhinitis and its Impact on Asthma: Management of allergic rhinitis symptoms in the pharmacy; A Pocket Guide for Pharmacists; 2003

[7] http://www.tga.gov.au/docs/pdf/medpreg.pdf

[8] ABS Health Literacy Australia 4233.0 2006 (updated June 2008): http://www.ausstats.abs.gov.au/Ausstats/subscriber.nsf/0/73ED158C6B14BB5ECA2574720011AB83/$File/42330_2006.pdf

[9] www.mimsonline.com.au

[redacted]

2.1.3 Ibuprofen - submission 1/2

XXXXX

20 January 2011

The Secretary
Medicines & Poisons Scheduling,
Office of Chemical Safety and Environmental Health (MDP 88)
GPO Box 9848, Canberra ACT 2601
Email: smp@health.gov.au

Fax: 02-6289 2500

Re: Meeting of the Advisory Committee on Medicines Scheduling – 23 February 2011 Additional items referred to the February 2011 meeting; Item 1.2 Ibuprofen – proposal to amend part (a) of the current Schedule 2 ibuprofen entry to increase the Schedule 2 limit on liquid preparations to at least 8 g or less (currently is 4 g or less)

The application to amend part (a) of the current Schedule 2 ibuprofen entry to increase the limit on liquid preparations to 8 g or less XXXXX is now scheduled for discussion at the forthcoming meeting of the ACMS on 23 February 2011. X XXXX would now like to take this opportunity to submit comment to the new ACMS.

The S2 classification of XXXXX 4% is currently limited to a pack size of 100 mL while there is no size restriction for paracetamol. According to the dosage recommendations, the pack size is not adequate for an average family with older aged children. XX XXX therefore requests the ACMS to consider increasing the pack size from 4g to 8g.

XXXXX would like to summarise the following matters under Section 52E of the Therapeutic Goods Act 1989 for the Committee's consideration:

(a) the risks and benefits of the use of a substance;

Ibuprofen is one of the most widely used NSAID in Australian children as it has been freely available over the counter since 1998[1]. It is second in-line therapy after paracetamol. The analgesic and antipyretic efficacy and ibuprofen compared to paracetamol were evaluated in a meta-analysis of eighty-five studies[2]. The results showed that ibuprofen is as or more efficacious than paracetamol for the treatment of pain and fever while there were no significant difference between ibuprofen and paracetamol in adverse event incidence.

xxxxx

[1] http://www.australianprescriber.com/magazine/31/3/63/5
[2] Pierce CA & Voss B. Efficacy and Safety of Ibuprofen and Acetaminophen in Children and Adults: A Meta-Analysis and Qualitative Review, Ann Pharmacother 2010; 44: 489-506

The major risk associated with ibuprofen is serious gastrointestinal complications. However, when compared to other NSAIDs e.g. ketoprofen, piroxicam, indomethacin, naproxen, sulindac and aspirin[3] and diclofenac[4], ibuprofen was associated with the lowest relative risk.

The Periodic Safety Update Report which covered XXXXX showed that the company received a total of XXXXX adverse events from XXXXX patients. Adverse events (AEs) were medically confirmed in 60 children ([redacted] adverse events) and not medically confirmed in XXXXX children (XXXXX AEs). The medically confirmed AEs in children in decreasing order were skin and subcutaneous disorders; gastrointestinal disorders; general disorders and administration site conditions; psychiatric disorders; and injury, poisoning and procedural complications. The AEs which were not non-medically confirmed were mainly accidental overdoses, followed by skin and subcutaneous disorders; gastrointestinal disorders; and psychiatric disorders. Of the XX XXX medically confirmed AEs, the gastrointestinal disorders consist of haematemesis (XXXXX), vomiting (XXXXX), lip oedema (XXXXX), abdominal pain upper (XXXXX), diarrhoea (XXXXX), gastrointestinal pain (XXXXX), gastrointestinal haemorrhage (XXXXX), tongue oedema (XXXXX), duodenal ulcer perforation (XXXXX), nausea (XXXXX), gastroenteritis (XXXXX), gastritis (XXXXX). Taking into account the number of units sold over this period and under-reporting of AEs, the incidence of gastrointestinal disorders is estimated to be very low.

(b) the purposes for which a substance is to be used and the extent of use of a substance

The approved indications are for the treatment of juvenile chronic arthritis, pyrexia including fever caused by immunisation, acute conditions associated with pain and/or inflammation such as teething, toothache, earache, headache, colds and flu, minor aches, sprains and strains and sore throats, and chronic conditions associated with pain and/or inflammation.

The label carries the following caution that: "*Excessive use can be harmful. For short term use only. If your child's symptoms persist for more than a few days consult your doctor. Children should take plenty of fluids.*"

[3] Henry D, Lim LL-Y, Rodrigues LAG, Gutthann SP, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S & Fries JT. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 1996; 312: 1563-1566

[4] http://www.nps.org.au/__data/assets/pdf_file/0007/15757/news02.pdf

(c) the toxicity of a substance

With paracetamol, liver damage is possible in adults who have taken 10g or more in adults and a single ingestion of 200 mg/kg[5]. Therapeutic dose of paracetanol in adult is 4 g per day. In contrast, poisoning guidelines[6] for ibuprofen suggest that ingestion of more than 400 mg/kg in children may cause symptoms. Based on the therapeutic dose of 10 mg/kg, the therapeutic index of ibuprofen is relatively wider than that of paracetamol.

Furthermore, the half-life for overdose is also relatively shorter and averaged from 1.9 to 2.2 hours. This eliminates the need of prolonged observation periods in cases of suspected poisoning.

(d) the dosage, formulation, labelling, packaging and presentation of a substance

The approved dosage recommendations of ibuprofen 10 mg/kg by the Medicines Evaluation Committee for children aged 6 to 12 years

In order to mitigate the risk of dosing errors, the XXXXX are specifically labelled to each of the age group:

1. **XXXXX " Babies 3+ months**" contains ibuprofen 4 % suspension so that a smaller volume needs be given and there is only one pack size of 50 mL.

2. **XXXXX "1-5 years"** contains ibuprofen 2% suspension and is available in pack sizes of 100 mL and 200 mL.

3. **XXXXX "5-12 years"** contains ibuprofen 4% suspension.

Since ibuprofen liquid preparations in S2 are limited to no more than 4 g of ibuprofen, the pack size for **XXXXX "5-12 years"** is limited to 100 mL. S 4 schedule applies to liquid preparations containing over 4 g of ibuprofen.

The labelling meets the TGO 69 (including RASML) with appropriate warnings and contra-indications for paracetamol and ibuprofen and will therefore be familiar to the responsible parents and carers of children.

(e) the potential for abuse of a substance

To date, there is no evidence that ibuprofen is associated with dependency, abuse or illicit use as an individual active.

XXXXX asserts that risk benefit profile for ibuprofen is comparable to that of paracetamol if used in accordance to the recommended dose and requests the Advisory Committee on Medicines Scheduling to consider increasing the pack size of ibuprofen in liquid preparations

[5] eTG Toxicology: paracetamol

[6] http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Informationforlicenceapplicants/Guidance/OverdosesectionsofSPCs/Genericoverdosesections/Ibuprofen/index.htm

of at least up to 8 g as the bottle size of 100 mL of 4% ibuprofen is n ot adequate to cover treatment for an average size family with older children.

Yours sincerely
XXXXX

XXXXX

Paediatric analgesia

Sean Beggs, General Paediatrician and Paediatric Clinical Pharmacologist, Royal Hobart Hospital, Hobart

Summary

Three main analgesics are routinely used for treating pain in children – paracetamol, ibuprofen and codeine. Paracetamol and ibuprofen are equally effective when used in recommended doses. Codeine has high inter-individual variation in its effectiveness, particularly in children, which significantly limits its routine use in paediatrics. Paracetamol is associated with fewer adverse effects than ibuprofen and so generally remains the first-line analgesic drug in children. However, paracetamol may not be the most appropriate choice in all patients depending on the type of pain being treated and the presence of comorbid illnesses. Paracetamol has unpredictable absorption with rectal administration so this route is no longer recommended. The combined use of paracetamol with non-steroidal anti-inflammatory drugs may be of benefit for some postoperative and musculoskeletal pain.

Key words: codeine, ibuprofen, NSAIDs, paracetamol.

(Aust Prescr 2008;31:63–5)

Introduction

In Australia, the main analgesic medications used in children in an ambulatory setting are paracetamol, ibuprofen and codeine. There has been significant debate in the literature recently as to which of these is the safest and most effective drug to use in children. In general these drugs are safe and effective when used at their recommended doses (Table 1). There are however a number of situations where one may be more appropriate than the other. Factors that need to be considered include the type of pain being treated, comorbidities and concomitant medication use. There are also situations when non-pharmacological methods may be the most appropriate form of intervention, either in isolation or in combination with drugs. This is often the situation in cases of chronic or recurrent pain.

Paracetamol

Paracetamol was discovered over 100 years ago and came into routine over-the-counter use approximately 40 years ago. Its popularity increased significantly in the 1980s when aspirin went out of favour due to its association with Reye's syndrome. Paracetamol is now the most widely used over-the-counter analgesic in children and is approved for use from one month of age. It is available over the counter in multiple paediatric dosage forms including liquids, chewable tablets and suppositories.

Mechanism of action

Despite being used so extensively, paracetamol's exact mechanism of action is still being debated. It has recently been postulated that it works through the inhibition of an isoenzyme of cyclo-oxygenase (COX)-3 that is only found in the brain and the spinal cord.[1] An alternative theory is that it works through the indirect activation of cannabinoid CB(1) receptors.[2] Regardless of this debate, the primary clinical outcome is that paracetamol increases pain tolerance via an effect in the central nervous system. Paracetamol is not an effective anti-inflammatory drug as it does not inhibit prostaglandin production outside the central nervous system, unlike non-steroidal anti-inflammatory drugs (NSAIDs).

Table 1

Recommended doses of paediatric paracetamol, ibuprofen and codeine [10]

Paracetamol	Ibuprofen	Codeine
Community setting		
15 mg/kg every 4–6 hours Maximum 4 doses (60 mg/kg) per day for up to 48 hours	5–10 mg/kg 3 or 4 times a day	0.5–1 mg/kg every 4–6 hours
Other settings		
Up to 90 mg/kg per day can be used under medical supervision with review after 48 hours Single doses of 30 mg/kg may be used for night-time dosing (do not exceed 60 mg/kg per 24 hours)	For juvenile rheumatoid arthritis 10 mg/kg 3 or 4 times a day	

Pharmacokinetics

Although paracetamol is available for administration via the oral, rectal and intravenous route, the oral route is preferred. The oral availability of paracetamol is approximately 90%. Its onset of action is approximately 30 minutes and duration of action is four hours. The rectal route is not recommended as absorption is highly variable and unpredictable, with the reported bioavailability ranging from 24% to 98%. The intravenous route is only used when the oral and rectal routes are not available, as may be the case in some inpatients postoperatively.

Efficacy

Paracetamol has repeatedly been shown in placebo-controlled clinical trials to be an effective analgesic in children with mild to moderate pain. It is effective for minor musculoskeletal pain, headaches including migraines, pain associated with infections such as otitis media and pharyngitis, and for postoperative pain after minor procedures such as adenotonsillectomies and insertion of ventilation tubes. It is not the most appropriate choice for pain that is associated with a significant inflammatory process, such as juvenile arthritis, when an NSAID is more suitable.

Safety

Paracetamol is a safe medication when used in the recommended doses. The main potential harm is liver toxicity (see box), which is caused by the accumulation of a toxic metabolite produced when the liver is depleted of glutathione. Relative to adults, children are less susceptible to acute toxic effects, but may be more susceptible to chronic exposure to paracetamol.

Malnutrition, starvation and intercurrent (febrile) illness increase the risk of liver toxicity. Acute toxicity occurs with paracetamol doses greater than 150 mg/kg. There have been reported cases of children developing liver toxicity who were said to be receiving therapeutic doses. These have tended to be overweight children who had prolonged courses, and were being dosed according to their actual weight, rather than their lean body weight. Children who are more than 20% above their ideal body weight should be dosed according to their lean body weight.[3] A quick conservative estimate of this can be obtained by determining their predicted weight for height (see Case example: Calculating lean body weight in obese children, on pages i and ii at the end of this article).

Drugs that induce cytochrome P450, such as phenobarbitone, phenytoin and rifampicin, increase the risk of liver toxicity.

Risk factors for acute toxicity with paracetamol

- Paracetamol doses greater than 150 mg/kg
- Incorrect dosing in overweight children
- Intercurrent (febrile) illness
- Malnutrition, starvation
- Drugs that induce cytochrome P450 (such as phenobarbitone, phenytoin, rifampicin)

The dose of paracetamol for obese children should be based on lean body mass

Ibuprofen

Ibuprofen is the most widely used NSAID in Australian children as it has been freely available over the counter since 1998. The approved minimum age has recently been reduced from six to three months of age. NSAIDs work by inhibiting COX and thus limiting the production of numerous prostaglandins involved in the inflammatory response.

Safety

NSAID-related adverse effects that occur in children are the same as those that occur in adults, but they seem to occur less often. These include increased gastrointestinal bleeding, reduced renal blood flow, reduced platelet function and bronchospasm in susceptible individuals. Compared to paracetamol, NSAIDs are associated with more frequent adverse events in children.[4]

The risk of renal toxicity is increased with situations that are associated with decreased renal perfusion, namely dehydration, hypovolaemia and hypotension. Pre-existing renal disease or the concomitant use of other nephrotoxic drugs, such as frusemide, aminoglycosides or ACE inhibitors, will also increase the risk of renal toxicity.

Another special group that is at increased risk of NSAID adverse effects are children with aspirin (or NSAID)-induced asthma. Again this entity is rarer in children than adults, however a recent study estimated the prevalence of ibuprofen sensitivity to be 2% in children with asthma.[5]

Codeine

Codeine has previously been recommended as an analgesic for mild to moderate pain in children.[6] It can be and has been given to children orally, rectally and by intramuscular or subcutaneous injection. In Australia, it is most often given in combination with a simple analgesic as part of an oral fixed-dose combination. Codeine is a weak opioid, with one-tenth the potency of morphine. It has its primary analgesic effects through being metabolised to morphine by the cytochrome P450 enzyme CYP 2D6. The popularity of codeine has been largely related to its perceived lower rate of toxicity compared with other opiates, despite there being relatively few studies of codeine's efficacy in children.

Safety

There is considerable inter-individual variation in the activity of CYP 2D6, with a significant and unpredictable number of individuals being poor metabolisers (7–30% depending on ethnicity) who are unable to benefit from codeine.[7] There is also a proportion of the population who are extensive metabolisers who produce significant amounts of morphine and are thus at increased risk of opioid adverse effects.

The activity of cytochrome P450 enzymes is very low at birth then increases with age. In the very young, CYP 2D6 activity is less than 1% of that in adults and is still less than 25% in children under five years of age.

The wide variation in individual metabolism and the unpredictable influence of age on the effectiveness and safety of codeine means that its routine use in children is not recommended. It can be argued that the use of a small dose of morphine is preferable to codeine as it is more effective and predictable.

Comparative studies

Numerous studies have compared paracetamol and ibuprofen in children. When the current recommended doses of both drugs were used (Table 1), efficacy was essentially the same.[8] A recent study in children with musculoskeletal injuries compared ibuprofen 10 mg/kg, paracetamol 15 mg/kg and codeine 1 mg/kg. Ibuprofen showed a statistically significant benefit over the other two drugs in children with fracture, but not in children with other minor soft tissue injury.[9] However, a significant weakness of the study was that 48% of the children in the paracetamol group received less than the standard dose of 15 mg/kg (as the maximum dose allowed was 650 mg), whereas only 22% of the patients in the ibuprofen group received less than the standard dose of 10 mg/kg (as the maximum dose allowed was 600 mg).

Multimodal analgesia

The evidence for combining paracetamol and NSAIDs in children for analgesia is conflicting. However, it appears that in a significant number of postoperative patients the combination can lead to a decreased need for morphine or other opioid analgesics. The combination of codeine with paracetamol or ibuprofen has not been well studied in children. There is evidence in adults that codeine can add significantly to the analgesic effects of paracetamol, NSAIDs and aspirin.[7] However, given the unpredictable and often poor efficacy of codeine in children, it is unlikely to add to the analgesic effects of paracetamol and NSAIDs.

Conclusion

Paracetamol and ibuprofen are safe and effective forms of analgesia in children. Paracetamol is generally the preferred first-line drug due to fewer adverse effects, however this will not be the case in all individuals, depending on the pain being treated and comorbidities. Codeine has a relatively unpredictable efficacy in children and is thus not routinely recommended. It should also be remembered that in some situations non-pharmacological methods may be the most appropriate treatment.

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Conflict of interest: none declared

Note: To calculate lean body weight, see case example and growth charts on pages i and ii at the end of this article.

Self-test questions

The following statements are either true or false (answers on page 83)

1. The dose of paracetamol for obese children should be based on lean body mass.
2. Paracetamol is the most effective analgesia for juvenile arthritis.

Case example: calculating lean body weight in obese children

Lean body weight calculation

Lean body weight (males) = (1.1 x weight) – (0.0128 x BMI x weight)

Lean body weight (females) = (1.017 x weight) – (0.0148 x BMI x weight)

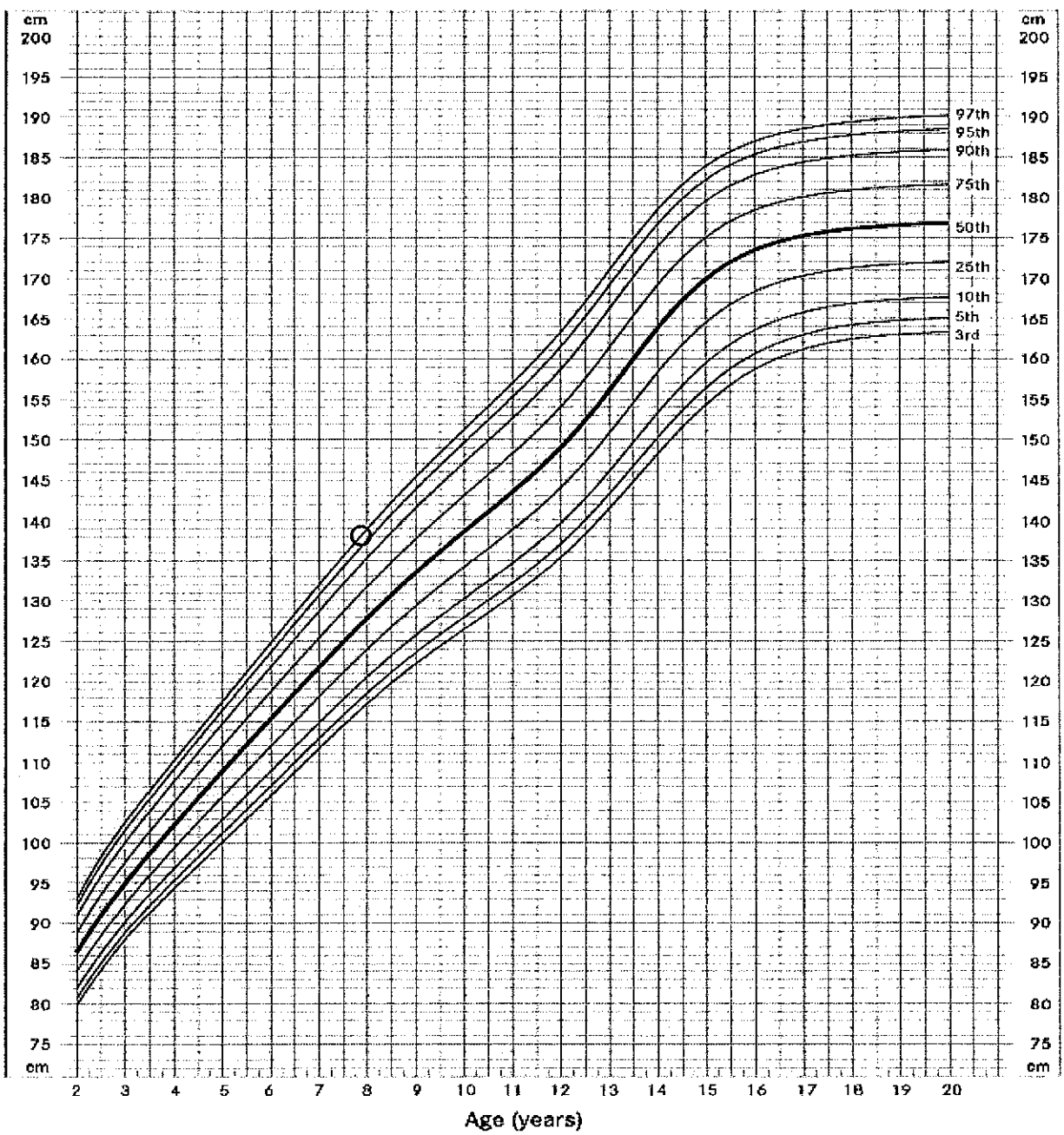
Body mass index (BMI) = weight (kg) / (height (m))^2

Weight for height

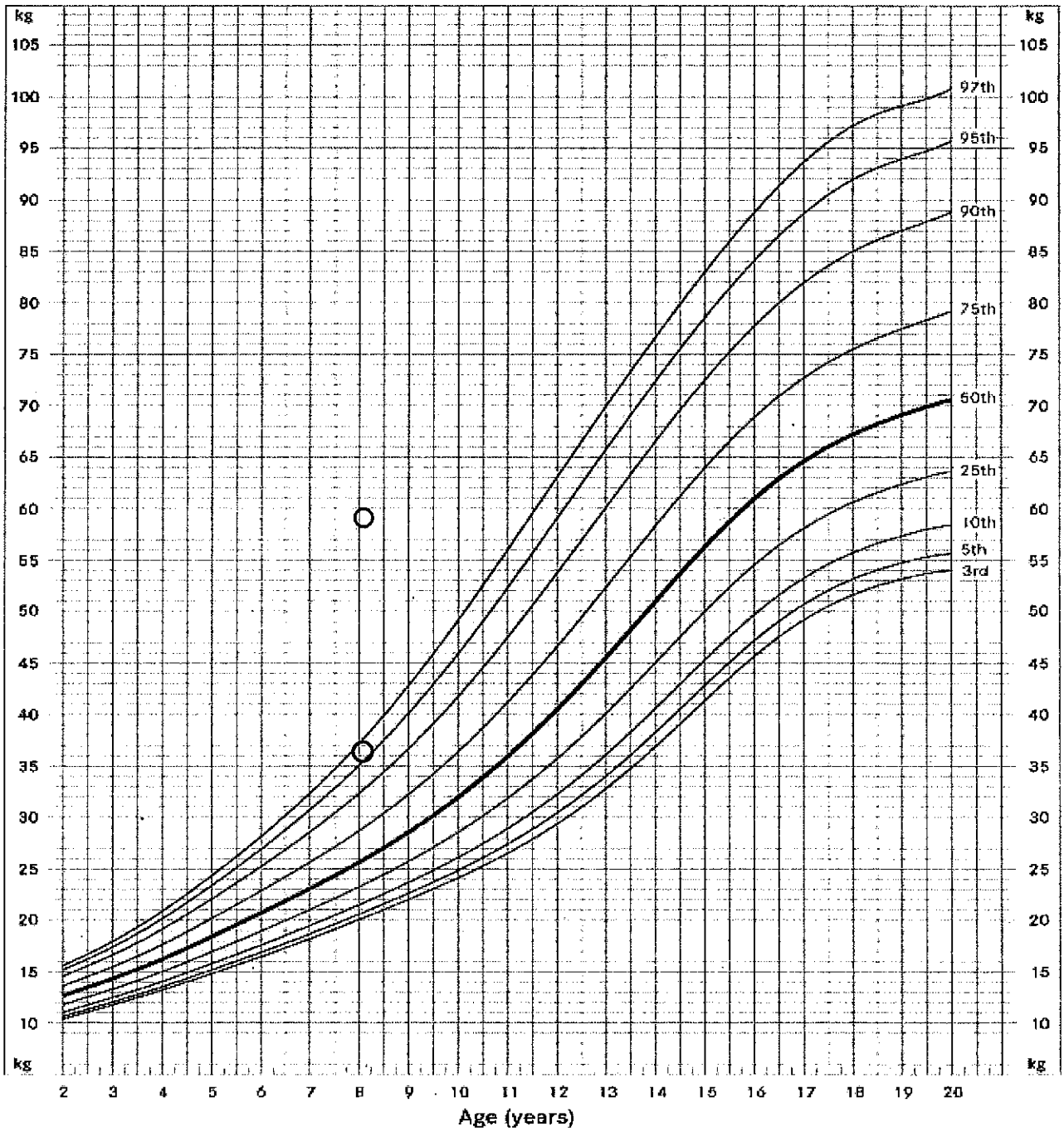
In this example an eight-year-old boy has a weight of 60 kg, and height of 138 cm which is on the 95th percentile for his age, thus his predicted weight for height is obtained by determining what weight corresponds to the 97th percentile for an eight-year-old boy, and here it is 35 kg. Therefore, his doses should be calculated using 35 kg, rather than 60 kg.

○ Actual weight and height ○ Predicted weight for height

Stature-for-age percentiles: Boys, 2 to 20 years



Weight-for-age percentiles: Boys, 2 to 20 years



Growth charts developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). The charts are available at www.health.vic.gov.au/childhealthrecord/growth_details/boys.htm

Efficacy and Safety of Ibuprofen and Acetaminophen in Children and Adults: A Meta-Analysis and Qualitative Review

Catherine A Pierce and Bryan Voss

OBJECTIVE: To evaluate the analgesic and antipyretic efficacy and safety of ibuprofen compared to acetaminophen in children and adults.

DATA SOURCES: Literature searches were performed using PubMed/MEDLINE (through August 2009) and EMBASE (through January 2008) and were restricted to the English language. In PubMed/MEDLINE, search terms used were ibuprofen, acetaminophen, paracetamol, clinical trials, and randomized controlled trials. EMBASE search terms included ibuprofen and acetaminophen, restricted to human and clinical trials.

STUDY SELECTION AND DATA EXTRACTION: All English-language articles identified from the data sources were reviewed. Multiple review articles were studied for any pertinent references and this yielded additional articles. Only articles that directly compared ibuprofen and acetaminophen were eligible for this review.

DATA SYNTHESIS: Eighty-five studies that directly compared ibuprofen to acetaminophen were identified; 54 contained analgesic efficacy data, 35 contained antipyretic/temperature reduction data, and 66 contained safety data (some articles contained more than 1 type of data). Qualitative review of the literature revealed that, for the most part, ibuprofen was more efficacious than acetaminophen for the treatment of pain and fever in both pediatric and adult populations, and that these 2 drugs were equally safe. Meta-analyses on the subset of randomized clinical trial articles that reported sufficient quantitative information to calculate either an odds ratio (adverse event [AE]) or standardized mean difference (pain and fever) confirmed the qualitative results for adult (standardized mean difference [SMD] 0.69; 95% CI 0.57 to 0.81) and pediatric (SMD 0.28; 95% CI 0.10 to 0.46) pain at 2 hours postdose and pediatric fever (SMD 0.26; 95% CI 0.10 to 0.41) at 4 hours postdose. Conclusions regarding adult fever/temperature reduction could not be made due to a lack of evaluable data. The combined odds ratio for the proportion of adult subjects experiencing at least 1 AE slightly favored ibuprofen; however, the difference was not statistically significant (1.12; 95% CI 1.00 to 1.25). No significant difference between drugs in AE incidence was found for pediatric patients (0.82; 95% CI 0.60 to 1.12).

CONCLUSIONS: Ibuprofen is as or more efficacious than acetaminophen for the treatment of pain and fever in adult and pediatric populations and is equally safe.

KEY WORDS: acetaminophen, adults, children, efficacy, ibuprofen, paracetamol, safety.

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Widespread use of ibuprofen and acetaminophen for the treatment of pain and fever in both children and adults has been common for more than 30 years.[1] Recently, the safety of acetaminophen was the subject of a 2-day Food and Drug Administration (FDA) advisory panel meeting.[2] Interestingly, while these drugs are used more frequently than any other over-the-counter analgesic or antipyretic, their relative efficacy and safety in adults has not been compared across the existing studies.

By compiling and comparing the efficacy and safety data from the available clinical studies that directly compare ibuprofen and acetaminophen, a broader conclusion than can be arrived at by assessing the data generated by any single study published to date may be possible. Previous meta-analyses/systematic reviews comparing the efficacy and safety of ibuprofen and acetaminophen have been completed in children.[3,4] These studies found that in children, ibuprofen was slightly more efficacious for pain and fever than was acetaminophen and that there were no differences in terms of safety.[3,4] However, a meta-analysis has not been completed in adults.

Therefore, we completed an analysis of the literature comparing the relative

Author information provided at end of text.

analgesic and antipyretic efficacy, as well as safety, of ibuprofen and acetaminophen in adults. The current analysis updates previously reported data regarding the safety and efficacy of ibuprofen and acetaminophen in children, as well.

Methods

LITERATURE SEARCH PARAMETERS

Literature searches were performed using PubMed/MEDLINE (through August 2009) and EMBASE (through January 2008) and were restricted to the English language. In PubMed/MEDLINE, the MeSH query terms used were ibuprofen, acetaminophen (including the term paracetamol), and clinical trials in the 1 search and ibuprofen, acetaminophen, and randomized controlled trials as topic in another search. The literature search of EMBASE was performed and the parameters were set to the following: under drug search: ibuprofen and acetaminophen, restricted to: English only, human, clinical trials. Finally, multiple review articles were studied for any pertinent references and this yielded additional articles. Clinical trials included prospective and retrospective studies that provided efficacy and/or safety data for a direct comparison of ibuprofen and acetaminophen. This comprehensive literature search returned a total of 664 articles. Case reports, medical record studies, letters, commentaries, and review articles that did not contain original efficacy or safety data were excluded. A total of 10 references were removed from the analysis due to multiple publications of the same data.

Articles were classified as containing efficacy data, safety data, or both. The efficacy articles were further limited to studies in which the following were included: (1) a direct comparison of ibuprofen and acetaminophen in the treatment of pain and/or fever, (2) the dose, and (3) the method of pain or fever measurement. Pain and fever were defined by the authors of the individual studies. The safety articles were limited to clinical studies in which the safety or tolerability of ibuprofen and acetaminophen was directly compared in terms of adverse events (AEs). These criteria were chosen as the minimum data set needed to qualitatively compare ibuprofen and acetaminophen in terms of efficacy for the reduction of pain and fever and to compare their reported safety profiles.

Of the 664 publications, 85 studies were identified that presented analgesic, antipyretic, and/or safety data when comparing ibuprofen and acetaminophen directly. One additional article contained qualitative safety data but was not included in any analyses due to the lack of AE data. If either the ibuprofen or acetaminophen study arm involved concomitant medication use, such as codeine, other opioids, or other analgesics/antipyretics, those articles were excluded from the analysis. Of these 85 studies, 80 presented data for which a comparison of efficacy could be made. Further, 66 of the 85 studies presented safety data comparing ibuprofen and acetaminophen. Of the 80 studies presenting efficacy data, 54 studies presented an analgesic comparison between ibuprofen and acetaminophen and 35 presented an antipyretic or temperature reduction comparison between ibuprofen and acetaminophen.

QUALITATIVE REVIEW METHODS

The ibuprofen versus acetaminophen literature was separated into 3 categories: (1) studies that reported data on the treatment of pain, (2) studies that reported data on the treatment of fever, and (3) studies that reported data on safety. Individual references may have presented efficacy (either or both indications) and/or safety data. All pertinent data were extracted. The extracted data were further separated into pediatric and adult studies because adults are given a standard fixed dose, while pediatric patients are typically administered a dose based on their total body weight. Adults typically receive 400 or 800 mg of ibuprofen per dose or 500 or 1000 mg of acetaminophen per dose, not to exceed 3200 mg and 4000 mg per day, respectively. For this analysis, the distinction between pediatric and adult studies was based on how the study population was defined by the authors of the individual studies. The majority of the studies considered patients under the age of 18 to be children and those over the age of 18 to be adults. However, some "pediatric" studies involved a few patients up to 19 years of age, while some "adult" studies involved a few patients as young as 15 years of age.

AEs and serious adverse events (SAEs) were defined and classified by the investigators of each respective study. All AE data reported by treatment group were extracted and captured in the safety database. If AE data were not reported, then this was captured as "NR" in the database. Articles that stated that no AEs occurred were captured as 0 AEs for the given patient population/treatment arm. The number of patients experiencing at least 1 AE, as well as the total number of AEs per patient was tabulated for each article (if reported). If an article reported on more than 1 ibuprofen or acetaminophen treatment group, such as a low- and a high-dose group, the AE rates for both doses were combined.

Qualitative reviews of the data were based on pooling the overall conclusion(s) of the individual articles. These overall conclusions had to be supported by the data (significant p value(s) or confidence intervals) presented in the article; otherwise, ibuprofen and acetaminophen were deemed to be equally efficacious and/or safe.

META-ANALYSIS METHODS

Meta-analyses were conducted to combine information across studies on the magnitude and direction of treatment effects for pain, fever, and AEs separately. For the meta-

analyses, only studies that were explicitly noted to be randomized trials with both an acetaminophen and ibuprofen treatment arm were included. If a study had more than the 2 treatment arms of interest (eg, aspirin, placebo, codeine), data from these arms were ignored. Data summarized only graphically were not included in the meta-analysis due to the imprecision of reading the correct means and variability measures from graphs.

The planned summary safety outcomes of interest were the proportion of subjects experiencing at least 1 AE and the proportion experiencing at least 1 SAE. Rate computations were based upon using a safety population definition for the denominators (all subjects receiving at least 1 clinical trial medication). In some of the studies, no AEs were observed in either the acetaminophen or ibuprofen treatment groups and thus an odds ratio could not be computed (zero denominator).[5] However, the amended odds ratio adds 0.5 to each cell of the contingency table prior to computation of the odds ratio, making it a viable parameter for these analyses. Therefore, amended odds ratios were computed to compare the acetaminophen group to the ibuprofen group for the proportion of subjects experiencing at least 1 AE for each study. The numerator of the odds ratio was the odds of an AE in the acetaminophen group, and hence odds ratios less than 1 favor acetaminophen, while values greater than 1 favor ibuprofen. All final analyses were based on the natural log of the amended odds ratios. Funnel plots were created for the log-amended odds ratios to visualize patterns consistent with heterogeneity or publication bias. A statistical test for heterogeneity of odds ratios was conducted and, if not significant, an overall odds ratio was computed using the Mantel-Haenszel estimator. The Mantel-Haenszel is an estimator that gives more weight to odds ratios from larger studies and is preferentially used when some studies have zero or small cell frequencies. Forest plots were created to provide a visual summary of the study-specific and combined log-amended odds ratios.

All measurements of pain or fever over time were extracted when available. If pain was measured using more than 1 scale, such as a visual analog scale (VAS) and an ordinal scale, the continuous measure was preferentially utilized for analysis. For continuous measures of temperature or pain VAS scores, the standardized mean difference (SMD) using Hedges' g_u was computed for each study for all measurement times as the acetaminophen mean minus the ibuprofen mean, provided sufficient information was reported. Use of the SMD allows for the pooling of studies with different measures of the same conceptual outcome such as the VAS for pain and an ordinal pain scale; however, interpretation of the SMD becomes more difficult than simple mean differences. Positive SMDs indicate higher pain or temperature values in the acetaminophen group compared to the ibuprofen group. Funnel plots were created to visualize patterns consistent with heterogeneity and possible publication bias. A combined estimate of the SMD was computed using a weighted average of each study's SMD based upon Hedges' g_u measures. The combined estimate is a weighted average where each study's SMD is weighted by the inverse of its variance.[5] As the variance is a function of sample size, this means larger studies are given more weight than smaller studies. No fixed or random effects models evaluating sources of heterogeneity were undertaken, as the subsets of analyzable randomized studies were small.

Many of the pain and fever trials had outcomes measured repeatedly over time. The Cochran Collaborative suggests analyzing such data at an early, middle, and late time point.[6] For these meta-analyses, middle and long-term follow-up times were not feasible due to variability of follow-up times across studies and scarcity of complete data available. Thus, for these analyses, only one time was selected—an early time. For pain studies, the early time of 2 hours post first dose was utilized. If no 2-hour measurement of pain was taken, then the post baseline time nearest to the 2-hour time point was utilized. The 2-hour time point resulted in retaining the maximum number of studies in the pain meta-analyses. For fever, the 4-hour time point was selected for the early evaluation. Both the pain and temperature early time points occurred before any multiple dosing; hence, no adjustment or subgroup analyses were performed to determine the effect of multiple dosing on outcomes.

Results

ANALGESIC EFFICACY

Eighty-five studies were identified that presented analgesic, antipyretic, and/or safety data when comparing ibuprofen and acetaminophen directly.[7-91] Of these 85 studies, 54 presented data supporting ibuprofen analgesic efficacy (pain) compared to acetaminophen.[11,13,15-32,35,36,38-43,45,46,50,51,53-55,57-60,62,64-67,69-76,83,84] Of these 54 studies, 36 were conducted in adult patients and 18 in pediatric patients.

Adult Pain

Of the 36 adult pain studies, 29 studies used a single dose of up to 200–600 mg ibuprofen and 7 studies used at least 1 dose of more than 600 mg ibuprofen (Table 1).[16-18-21,23,25-30,32,35,36,40,42,45,50,51,53,54,57-60,64-67,70,71,73,74,76,83] The strength of acetaminophen used in these studies ranged from 500 to 1300 mg per dose. Analgesic models included episiotomy, oral surgery, joint pain, menstrual pain, headache, sore throat, cancer pain, hysterectomy, general postsurgical pain, and experimentally induced pain (pinching of the interdigital webs of the hands). Qualitative review of these studies found that 26 concluded that ibuprofen was superior to acetaminophen treatment, 10 found no significant difference (all data trends counted as equivocal), and

no studies concluded that acetaminophen was superior to ibuprofen. The results were consistent between the lower and higher ibuprofen dose groups.

For the adult pain studies, only 9 of the 36 studies were randomized controlled trials that had sufficient information to compute an SMD for pain at 2 hours.[18,20,23,45,51,54,57,74,83] None of the 9 analyzable studies had more than 1 acetaminophen or ibuprofen treatment group. Figure 1 shows a Forest plot of the SMD for each study, together with a weighted estimate of the overall SMD. The overall estimate was 0.69 (95% CI 0.57 to 0.81), indicating smaller pain scores for ibuprofen compared with acetaminophen at 2 hours postdose. Using Cohen's rules of thumb, 0.69 corresponds with a medium effect size.

For all efficacy measures, an analysis of variance model was utilized to test for heterogeneity of the SMDs. Due to the small number of studies included in each separate meta-analysis, further analyses relating the effect size estimates to study characteristics such as dose were not conducted.

Pediatric Pain

Eighteen studies contained data comparing the effect of ibuprofen to that of acetaminophen on pediatric pain.[11,13,15,17,22,24,31,38,39,41,43,46,55,62,69,72,75,84] The dose of acetaminophen used in these studies ranged from 10 to 40 mg/kg per dose. These 18 studies utilized analgesic models including dental/oral surgery, musculoskeletal trauma, myringotomy, sore throat, postsurgical pain, headache pain, pain upon vaccination, and discomfort in febrile children (Table 2). Studies involving ibuprofen and acetaminophen for pediatric analgesic efficacy concluded that ibuprofen was superior to acetaminophen treatment in 6 studies, there were no significant differences in 11 studies (all data trends counted as equivocal), and ibuprofen was superior to acetaminophen on the day of surgery but not different from acetaminophen on the days following surgery in 1 study (Table 2).

For the pediatric pain studies, 6 of the 18 studies were randomized controlled trials that had sufficient information to compute an SMD.[13,22,31,38,72,75] For the Gazal and Mackie article, only the higher acetaminophen dose treatment arm was included to avoid any possible correlation of SMDs within studies.[38] Figure 2 shows a Forest plot of the SMDs together with an overall weighted estimate of the SMDs. The overall weighted estimate was 0.28 (95% CI 0.10 to 0.46), indicating superior pain relief in the ibuprofen-treated children 2 hours after dosing. The weighted estimate of 0.28 is consistent with Cohen's small effect size estimates.

ANTIPYRETIC EFFICACY

To evaluate the efficacy of ibuprofen and acetaminophen in the treatment of fever, the 35 articles containing fever/temperature reduction data were separated into 2 groups, adult studies and pediatric studies.[7,8,10-12,14,15,33,34,41,43,44,47-50,53,56,63,68,70,71,75,77-82,85-90] Five articles contained adult temperature reduction data, while 30 articles contained pediatric fever data.

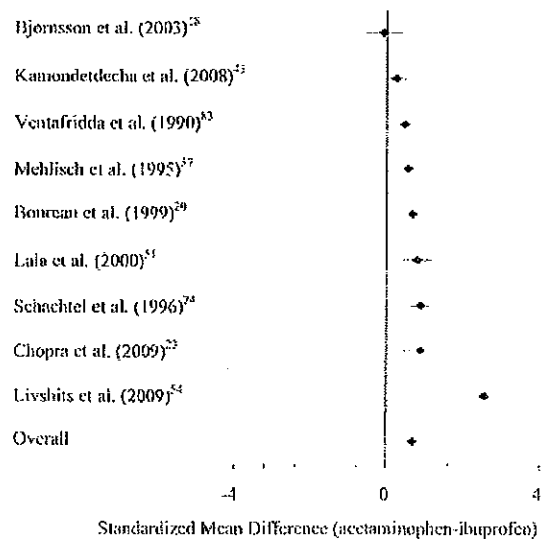

Figure 1. Forest plot of standardized mean difference of pain measurement for acetaminophen versus ibuprofen in adults. Negative numbers denote acetaminophen treatment group had lower pain measures than the ibuprofen groups.

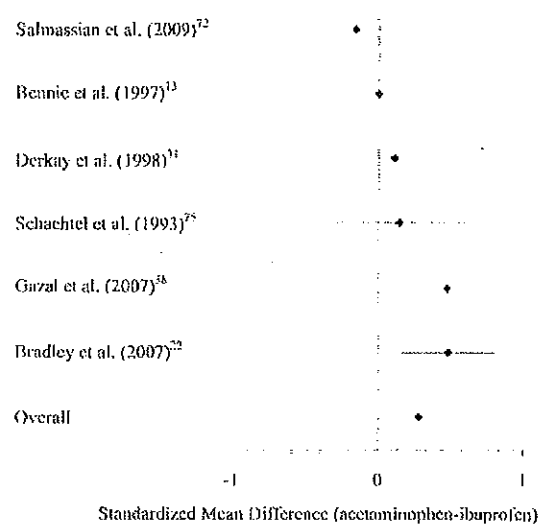

Figure 2. Forest plot of standardized mean difference of pain measurement for acetaminophen versus ibuprofen in children. Negative numbers denote acetaminophen treatment group had lower pain measures than the ibuprofen groups.

Adult Temperature Reduction

Of the 5 studies that presented adult temperature reduction data, 3 studies concluded that ibuprofen was superior to acetaminophen treatment, while 2 studies showed no significant difference (Table 3).[33,50,53,70,71]

However, for the adult temperature reduction studies, only 1 of 5 had sufficient information reported to compute an SMD, and thus a meta-analysis for adult temperature reduction data was not possible.

Pediatric Fever

Thirty studies reported pediatric fever data (Table 4).[7,8,10-12,14,15,34,41,43,44,47-49,56,63,68,75,77-82,85-90] In summary, 15 studies involving ibuprofen compared to acetaminophen for pediatric antipyretic efficacy concluded that ibuprofen was superior to acetaminophen treatment, while no significant differences were found in the remaining 15 studies.

For the pediatric fever studies, only 7 of the 30 studies were randomized controlled trials that had sufficient information to compute an SMD.[8,10,34,41,80-82] Figure 3 shows a Forest plot of the SMD together with an overall weighted estimate of the SMD. The overall estimate was 0.26 (95% CI 0.10 to 0.41), indicating significantly better fever control for ibuprofen at 4 hours postdose compared with acetaminophen. The SMD of 0.26 is consistent with a small effect size using Cohen's rules of thumb.

SAFETY

Sixty-six articles contained safety data in terms of AEs.[7-12,14-16,18-21,24-29,31-33,35,37,39,41,42,44,45,47,50-53,55-62,64-68,70,71,73-76,78-87,89-91] Thirty-five articles contained adult safety data and 31 articles contained pediatric safety data. Adverse events ranged from mild to severe and included any untoward events described by the authors of the individual studies. More than 30 different AEs occurred across the studies combined, ranging from nausea to urticarial rash to pneumopathy requiring hospitalization. One additional article contained qualitative safety data but was not included in any analyses.[92]

Adult Adverse Events

Thirty-five articles contained adult safety data and were reviewed.[16,18-21,25-29,32,33,35,37,42,45,50,51,53,57-61,64-67,70,71,73,74,76,83,91] Qualitatively, none of these studies found a significant difference in the safety of ibuprofen compared to acetaminophen.

Twenty-five of the 35 studies were randomized controlled trials that provided sufficient information to compute the odds of a subject experiencing at least 1 AE for the acetaminophen versus ibuprofen treatment arms.[19,20,25,29,33,35,37,42,45,50,51,57-59,61,64-67,70,71,73,74,76,91] The test for heterogeneity of odds ratios was not significant. The summary Mantel-Haenszel odds ratio was 1.12 (95% CI 1.00 to 1.25), showing a slight difference between the odds of at least 1 AE for acetaminophen compared with ibuprofen in adults. Using Cohen's rules of thumb for interpreting effect size estimates, the combined estimate represents a small effect. Plots of the study-specific and combined amended natural log odds are shown in Figure 4.

Pediatric Adverse Events

Thirty-one articles reported pediatric safety data and were qualitatively reviewed.[7-12,14,15,24,31,39,41,44,47,52,55,56,62,68,75,78-82,84-87,89,90] Qualitatively, 30 of those articles did not find a statistically significant difference between ibuprofen and acetaminophen, while 1 article, by Autret et al., reported that acetaminophen was safer or better tolerated than ibuprofen.[11]

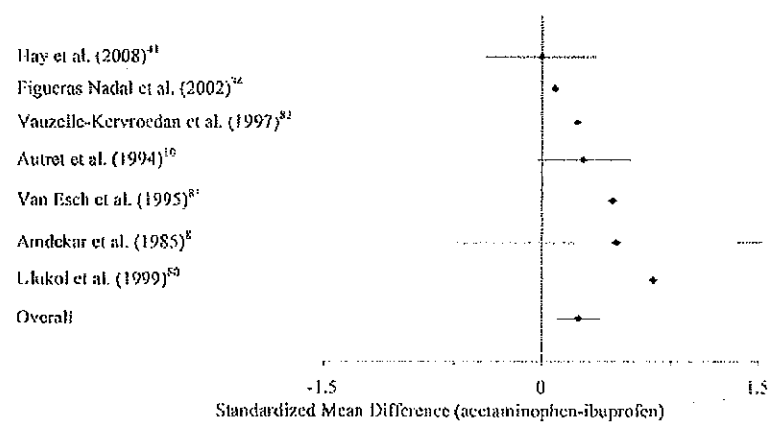

Figure 3. Forest plot of standardized mean difference of fever for acetaminophen versus ibuprofen in children. Negative numbers denote acetaminophen treatment group had higher temperature measures than the ibuprofen groups.

Of the 31 pediatric safety citations, 19 were randomized controlled trials that reported sufficient data on the number or proportion of subjects experiencing 1 or more AEs, allowing computation of an odds ratio.[7,8,10-12,14,15,24,34,47,55,56,62,68,75,78,80,82,85] The test for heterogeneity of odds ratios was not significant, and the combined estimate of the odds ratio was 0.82 (95% CI 0.60 to 1.12), failing to show a significant difference in the proportion of pediatric subjects experiencing 1 or more AEs in the 2 treatment arms. Figure 5 shows the study-specific and combined amended odds ratio estimators on the natural log scale.

Serious Adverse Events

Within the subset of randomized studies, a total of only 3 SAEs were reported: 1 in an adult study and 2 in pediatric studies. As so few serious AEs were reported, the combined odds ratio for SAEs was not computed. The small number of total SAEs reported is consistent with the short duration of the included clinical trials.

Qualitatively, none of the studies found a difference in the incidence of SAEs between ibuprofen- and acetaminophen-treated patients.

Limitations of Studies

Some methodological limitations may complicate the interpretation of the results of this analysis. Since only articles written in English were included in the analysis, it is possible that pivotal studies in non-English journals may exist and these articles could theoretically contain data that were different from those summarized within this meta-analysis. While the data abstraction process was both fair and consistent, issues regarding AE/SAE tabulation did arise. For instance, since we did not conduct the clinical studies ourselves, we had to rely on the investigators' definitions of AEs and SAEs, and that could have limited AE/SAE reporting. Additionally, the AE and SAE data were not always presented in the articles in a clear, thorough manner, as some articles reported only SAEs but did not report AEs. Many reports gave the total number of AEs or possibly related AEs and not the number of subjects experiencing at least 1 AE. The proportion of safety reports that could be utilized in the meta-analysis was small and may bias results. Further, the comparison of AE rates ignores any drug-specific expected AE profiles, such as liver function abnormalities or gastrointestinal (GI) bleeding/ulceration.

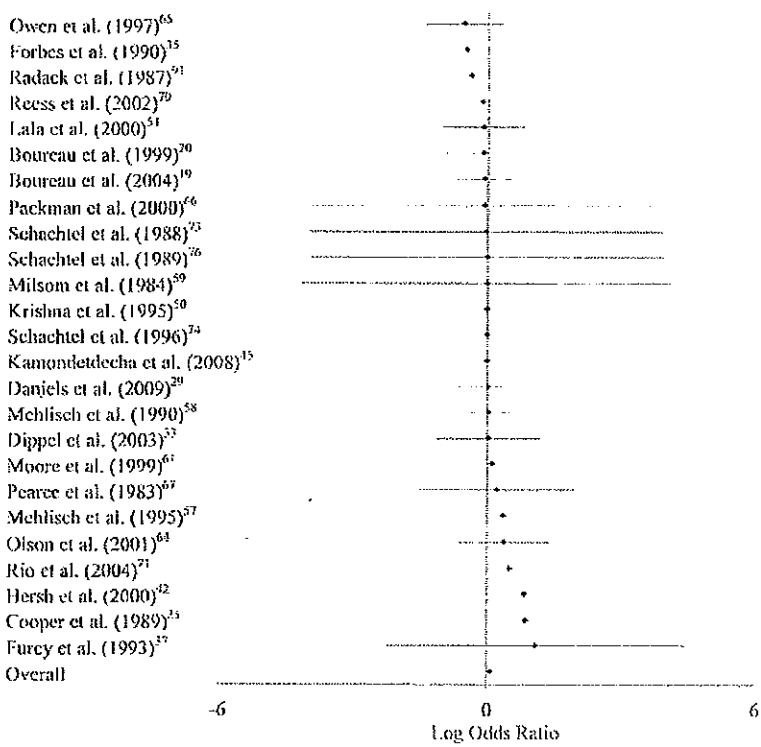

Figure 4. Forest plot of amended log odds ratios comparing proportion of adults experiencing at least one adverse event for acetaminophen versus ibuprofen. Negative numbers denote that the odds in the acetaminophen treatment group are lower than the ibuprofen groups.

Another limitation of this review was that we did not include case reports or case series in our safety analyses. However, since case reports and case series typically involve only small numbers of patients, it is unlikely that including those data would have changed the statistical analyses or outcomes. Additionally, by including only direct-comparison studies, rare AEs may not have been observed.

While the treatment groups were well controlled in the randomized studies, there is considerable clinical heterogeneity when comparing the individual studies to one another. These differences can add difficulty to interpretation of this analysis, while simultaneously strengthening the findings by showing that the safety and potency of the drugs are similar across patients of differing age, sex, ethnicity, and type of illness. In addition, the randomized studies included in this meta-analysis were typically short; thus, inference to chronic ibuprofen and acetaminophen use is not reasonable and the data did not allow for multiple time points posttreatment to be quantitatively summarized.

Lastly, analyses were based only on the published reports. Investigators were not contacted to obtain data that were missing from the reports.

Discussion

Previous meta-analyses and systematic reviews have only assessed the efficacy and safety of ibuprofen versus acetaminophen in children, while data for adults have not been analyzed.[3,4] This report updates and reiterates the findings of the previous pediatric analyses, while adding an analysis of the efficacy and safety of ibuprofen compared to acetaminophen in the adult population.

Qualitative review and quantitative analyses of evaluable clinical trials published in the medical literature showed that ibuprofen was as or more efficacious than acetaminophen for the treatment of pain and fever in pediatric patients and of pain in adult patients. There were not enough data to make a quantitative comparison of adult temperature reduction by ibuprofen compared to acetaminophen, but the qualitative review showed that ibuprofen was as or more efficacious than acetaminophen for reducing temperature in adults. Interestingly, no individual literature reference presented the overall conclusion that acetaminophen was superior to ibuprofen in terms of either analgesic or antipyretic efficacy in children or adults.

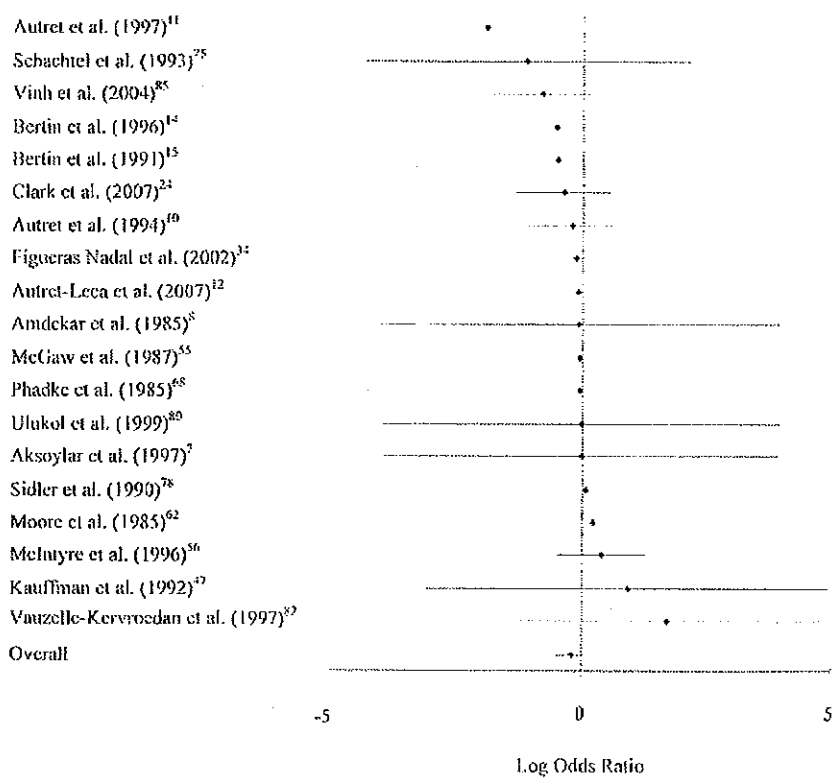

Figure 5. Forest plot of amended log odds ratios comparing proportion of children experiencing at least one adverse event for acetaminophen versus ibuprofen. Negative numbers denote that the odds in the acetaminophen treatment group are lower than the ibuprofen groups.

Table 1. Adult Pain Data

Reference	Design and Dose	Overall Conclusion
Ibuprofen doses 200–600 mg		
Bhounsule (1990)[16]	N = 60[a] Ibuprofen 400 mg vs acetaminophen 500 mg vs aspirin 600 mg vs metamizole 500 mg vs placebo in women 24 h after uncomplicated child delivery for analgesia	Ibuprofen more efficacious than acetaminophen, metamizole, aspirin, or placebo (pain scores significantly in favor of ibuprofen over first 6 h)
Bjornsson (2003)[18]	N = 72 Ibuprofen 600 mg 4 times/day vs acetaminophen 1000 mg 4 times/day in adults aged 19–27 y for treatment of pain following oral surgery	Ibuprofen and acetaminophen equally alleviated pain and swelling following oral surgery
Boureau (1999)[20]	N = 113 Ibuprofen 400 mg 3 times/day vs acetaminophen 1000 mg 3 times/day in adults for treatment of sore throat pain	Ibuprofen more efficacious than acetaminophen (sore throat pain relief ratings significantly in favor of ibuprofen)
Boureau (2004)[19]	N = 222 Ibuprofen 400 mg vs acetaminophen 1000 mg in adults aged 50–85 y single dose and 3 times/day for analgesia of osteoarthritic knee or hip	Ibuprofen more efficacious then acetaminophen (pain scores significantly in favor of ibuprofen over first 6 h and following multiple doses)
Bradley (1991)[21]	N = 184 Ibuprofen 300 or 600 mg 4 times/day vs acetaminophen 1000 mg 4 times/day in adults ≥30 y of age for treatment of chronic knee pain	Overall, ibuprofen and acetaminophen equally alleviated pain and swelling following oral surgery; however, ibuprofen was more efficacious than acetaminophen for pain at rest, according to rest pain scores
Chopra (2009)[23]	N = 90[a] Ibuprofen 600 mg 3 times/day vs acetaminophen 1000 mg 3 times/day vs betamethasone 0.5 mg 3 times/day vs serratiopeptidase 20 mg 3 times/day vs placebo 3 times/day for treatment of pain in adults aged 18–45 y undergoing surgery for a unilateral impacted third molar	Ibuprofen more efficacious than acetaminophen, serratiopeptidase, and placebo on days 3 and 4 following the surgery; acetaminophen was not found to be more efficacious than placebo at any point during the study
Cooper (1989)[25]	N = 184[a] Ibuprofen 400 mg vs acetaminophen 1000 mg vs placebo in pts. ≥16 y old for treatment of pain following oral surgery	Ibuprofen more efficacious than acetaminophen or placebo (pain scores significantly in favor of ibuprofen over first 6 h)
Dalton (2006)[28]	N = 255 Ibuprofen 400 mg 3 times/day vs acetaminophen 1300 mg 3 times/day in patients ≥18 y old for treatment of pain due to sprained ankle	Ibuprofen and acetaminophen equally efficacious in the relief of sprained ankle pain
Daniels (2009)[29]	N = 321[a] Ibuprofen 400 mg (standard and experimental formulations) vs acetaminophen 1000 mg in adults 16–40 y old for treatment of postoperative dental pain	Both formulations of ibuprofen more efficacious than acetaminophen for treatment of postoperative dental pain
Dawood (2007)[30]	N = 30[a] Ibuprofen 400 mg 4 times/day vs acetaminophen 1000 mg 4 times/day vs placebo 4 times/day in middle-aged women for treatment of menstrual pain	Ibuprofen and acetaminophen equally efficacious in the relief of menstrual pain compared to placebo
Forbes (1990)[35]	N = 43 Ibuprofen 400 mg vs acetaminophen 600 mg vs acetaminophen 600 mg with codeine vs ketorolac 10 or 20 mg vs placebo in pts. ≥15 y old for treatment of pain following oral surgery	Efficacy of ibuprofen and ketorolac was similar but ibuprofen was more efficacious than acetaminophen, acetaminophen with codeine, or placebo (pain relief scores significantly in favor of ibuprofen over first 6 h)
Harris (2003)[40]	N = 74 Ibuprofen 400 mg vs acetaminophen 1000 mg in middle-aged adults for the treatment of headache pain associated with high altitudes	Ibuprofen and acetaminophen equally reduced high-altitude headache
Hersh (2000)[42]	N = 210[a] Ibuprofen 200 or 400 mg vs acetaminophen 1000 mg vs placebo in pts. ≥16 y old for treatment of pain following oral surgery	Ibuprofen more efficacious than acetaminophen or placebo (time to onset, magnitude, and duration of pain relief significantly in favor of ibuprofen)
Kamondetdecha (2008)[45]	N = 210 Ibuprofen 400 mg vs acetaminophen 1000 mg in women for treatment of pain associated with childbirth	Ibuprofen more efficacious than acetaminophen 1 h after treatment; the 2 drugs were equivalent after 2 h
Lala (2000)[51]	N = 113 Ibuprofen 400 mg vs acetaminophen 1000 mg in middle-aged adults for treatment of pain associated with tonsillopharyngitis	Ibuprofen more efficacious than acetaminophen (pain scores significantly in favor of ibuprofen)

Livshits (2009)[64]	N = 120 Ibuprofen 400 mg vs acetaminophen 500 mg in women 18–35 y old for treatment of pain associated with first-trimester abortion	Ibuprofen more efficacious than acetaminophen for the treatment of pain following medical abortion
Mehlisch (1990)[58]	N = 697[a] Ibuprofen 400 mg vs acetaminophen 1000 mg vs placebo in middle-aged adults for treatment of pain following oral surgery	Ibuprofen more efficacious than acetaminophen (pain scores significantly in favor of ibuprofen over first 6 h)
Mehlisch (1995)[57]	N = 239[a] Ibuprofen 400 mg vs acetaminophen 1000 mg vs placebo in pts. ≥15 y old for treatment of pain following oral surgery	Ibuprofen more efficacious than acetaminophen (pain scores significantly in favor of ibuprofen over first 6 h)
Milsom (1984)[59]	N = 8 Ibuprofen 400 mg vs acetaminophen 500 mg vs naproxen 250 mg in young women for treatment of menstrual pain	Ibuprofen more efficacious than acetaminophen or naproxen (pain scores significantly in favor of ibuprofen 1.5 h after medication)
Molla (1974)[60]	N = 126 Ibuprofen 400 mg 3 times/day vs acetaminophen 1000 mg 3 times/day in women 14–26 y old for treatment of menstrual pain	Ibuprofen and acetaminophen equally efficacious in the relief of menstrual pain
Olson (2001)[65]	N = 172[a] Ibuprofen 400 mg vs acetaminophen 1000 mg vs ketoprofen 25 mg vs placebo in pts. 16–65 y old for treatment of pain following oral surgery	Ibuprofen more efficacious than acetaminophen or ketoprofen (pain scores and percentage of pts. requiring rescue medications significantly in favor of ibuprofen 1.5 h after medication)
Packman (2000)[66]	N = 154[a] Ibuprofen 400 mg vs acetaminophen 1000 mg vs placebo in middle-aged adults for treatment of tension-type headache pain	Ibuprofen more efficacious than acetaminophen or placebo (pain scores significantly in favor of ibuprofen 0.5–3 h after medication)
Pearce (1983)[67]	N = 49 Ibuprofen 400 mg 4–6 times/day vs acetaminophen 900 mg 4–6 times/day in pts. ≥18 y old for treatment of migraine headache	Ibuprofen more efficacious than acetaminophen (ibuprofen superior to acetaminophen for reduction of headache duration and severity, and ibuprofen was more preferred)
Reess (2002)[70]	N = 104 Ibuprofen 400 mg 4 times/day vs acetaminophen 1000 mg 4 times/day in pts. taking IFN beta-1a for MS for treatment of IFN-mediated adverse effects of fever and headache	Ibuprofen and acetaminophen were equally efficacious in the relief of headache
Rio (2004)[71]	N = 56 Ibuprofen 400 mg 3 times/day vs acetaminophen 500 mg 3 times/day vs 60 mg prednisone once a day in pts. ≥18 y old taking IFN beta-1a for MS for treatment of IFN-mediated adverse effects such as fever and headache	Ibuprofen and prednisone superior to acetaminophen for the relief of headache on the day of IFN beta-1a injection, but none of the treatments were efficacious on the days following the injection
Schachtel (1988)[73]	N = 120[a] Ibuprofen 400 mg vs acetaminophen 1000 mg vs placebo in middle-aged adults for treatment of sore throat pain	Ibuprofen more efficacious than acetaminophen or placebo (pain scores significantly in favor of ibuprofen for both moderate and severe pain)
Schachtel (1989)[75]	N = 111[a] Ibuprofen 400 mg vs acetaminophen 1000 mg vs placebo in women for treatment of postpartum episiotomy pain	Ibuprofen more efficacious than acetaminophen or placebo (pain scores significantly in favor of ibuprofen)
Schachtel (1996)[74]	N = 455[a] Ibuprofen 400 mg vs acetaminophen 1000 mg vs placebo in pts. ≥18 y old for treatment of tension-type headache pain	Ibuprofen more efficacious than acetaminophen or placebo (pain scores significantly in favor of ibuprofen)
Ventafridda (1990)[83]	N = 31 Ibuprofen 600 mg vs acetaminophen 500 mg vs aspirin 600 mg 3 times/day vs diclofenac 100 mg 2 times/day vs indomethacin 50 mg 3 times/day vs pirprofen 400 mg 3 times/day vs sulindac 300 mg 2 times/day vs naproxen 250 mg 3 times/day vs suprofen 200 mg 3 times/day in older adults for treatment of cancer pain	Ibuprofen and acetaminophen equally efficacious in the relief of cancer-associated pain, but naproxen, diclofenac, and indomethacin were slightly more effective

IFN = interferon; MS = multiple sclerosis.
[a]N includes patients in the placebo group.

(continued on page 498)

Table 1. Adult Pain Data (continued)

Reference	Design and Dose	Overall Conclusion
Ibuprofen doses >600 mg		
Dahl (1997)[27]	N = 66[a] Ibuprofen 800 mg vs acetaminophen 1000 mg vs placebo in women for treatment of hysterectomy pain	Ibuprofen and acetaminophen had a comparable lack of analgesic effect when compared to placebo
Dahl (2004)[28]	N = 37 Ibuprofen 800 mg 3 times/day vs acetaminophen 1000 mg 3 times/day vs ibuprofen 800 mg/acetaminophen 1000 mg combination 3 times/day in young adults for treatment of pain after reconstructive ACL surgery	Ibuprofen and ibuprofen/acetaminophen more efficacious than acetaminophen alone for pain reduction and reduction of rescue opioid use
Dionne (1983)[32]	N = 107[a] Ibuprofen 800 mg loading dose, followed by 2 ibuprofen 400-mg doses vs acetaminophen 600 mg (same dosing schedule as ibuprofen) vs acetaminophen with codeine 600 mg (same dosing schedule as ibuprofen) vs placebo (same dosing schedule as ibuprofen) in young, otherwise healthy patients for treatment of pain following oral surgery	Ibuprofen more efficacious than acetaminophen, acetaminophen with codeine, or placebo for pain relief
Forster (1992)[36]	N = 60[a] Ibuprofen 800 mg vs acetaminophen 1000 mg vs dipyrone 1000 mg vs placebo in adults 24–33 y old for treatment of experimentally induced pain	Ibuprofen and dipyrone more efficacious than acetaminophen or placebo (pain rating significantly in favor of ibuprofen)
Krishna (1995)[50]	N = 16 Ibuprofen 10 mg/kg vs acetaminophen 15 mg/kg in non-pregnant adults for treatment of malarial fever and headache	Ibuprofen more efficacious than acetaminophen (headache responded to ibuprofen longer and more frequently than acetaminophen)
Leuschen (2004)[52]	N = 19 Ibuprofen 600 or 800 mg 3 times/day vs acetaminophen 1000 mg 4 times/day vs naproxen 400 mg 2 times/day in pts. 19–65 y old taking IFN beta-1a for MS for treatment of IFN-mediated adverse effects such as fever and headache	Ibuprofen and naproxen more efficacious than acetaminophen for reduction of headache associated with IFN beta-1a injection
Owen (1997)[65]	N = 90 Ibuprofen 1600 mg once a day vs acetaminophen 1000 mg 4 times/day in pts. 18–75 y old for treatment of pain following gallbladder surgery	Ibuprofen and acetaminophen equally efficacious in the relief of pain, reduction of rescue opioid use, and the overall evaluation; however, the data showed a strong trend toward ibuprofen being more efficacious than acetaminophen

ACL = anterior cruciate ligament; IFN = interferon; MS = multiple sclerosis.
[a]N includes patients in the placebo group.

Qualitative review and quantitative analyses also found no significant difference in proportions of subjects experiencing an AE, demonstrating that ibuprofen and acetaminophen are equally safe. Known AEs of nonsteroidal antiinflammatory drugs such as ibuprofen are upper GI bleeding and a cardiovascular risk. These effects are typically associated with long-term use. Liver toxicity is typically the main concern with acetaminophen overdose, either intentional or unintentional. The safety of acetaminophen was recently addressed by a 2-day FDA advisory panel meeting.[2] The advisory panel voted to recommend lowering the maximum daily dose of nonprescription acetaminophen, which is currently 4 g. The panel was not asked to recommend another maximum daily dose. The panel also voted to recommend that the maximum single dose of acetaminophen be limited to 650 mg and that the 1000-mg dose of acetaminophen be available only by prescription. However, the FDA is not obligated to follow the recommendations of its advisory panels. These measures are aimed at reducing the number of cases of accidental acetaminophen overdose caused by misuse and/or unknowing overuse of the product.[93] The prevalence of accidental overuse/overdose has only become more common in recent years as more and more combination products contain acetaminophen.[93] Although advances have been made in treating this condition, it still can result in severe hepatotoxicity and death.[93]

Health professionals should consider these compelling data when choosing one of these agents for treatment of pain and fever in adults and children.

This analytical review demonstrates that ibuprofen is as or more efficacious than acetaminophen for the treatment of pain and fever in both children and adults and that the 2 drugs are equally safe.

Catherine A Pierce PharmD, Pharmaceutical Care Coordinator—Critical Care, Critical Care Specialty Residency Director, Department of Pharmacy, Wake Forest University Baptist Medical Center, Winston-Salem, NC

Bryan Voss PhD, Research Associate, Cumberland Pharmaceuticals Inc., Nashville, TN

Reprints: Dr. Pierce, Department of Pharmacy, Wake Forest University Baptist Medical Center, Medical Center Blvd., Winston-Salem, NC 27157, fax 336/317-3401, capierce@wfubmc.edu

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Table 2. Pediatric Pain Data

Reference	Design and Dose	Overall Conclusion
Autret (1997)[11]	N = 228 Ibuprofen 7.5 mg/kg vs acetaminophen 10 mg/kg vs aspirin 10 mg/kg in febrile children aged 6–24 mo for analgesic and antipyretic efficacy and comfort	Ibuprofen more efficacious than acetaminophen or aspirin (comfort scores significantly in favor of ibuprofen 6 h after first dose of treatment)
Bennie (1997)[13]	N = 43[a] Ibuprofen 10 mg/kg vs acetaminophen 15 mg/kg vs placebo in children ≥6 mo for treatment of pain following myringotomy	Neither ibuprofen nor acetaminophen more efficacious than placebo for the treatment of pain following myringotomy
Bertin (1991)[15]	N = 231[a] Ibuprofen 10 mg/kg 3 times/day vs acetaminophen 10 mg/kg 3 times/day vs placebo 3 times/day in children 6–12 y old for treatment of sore throat pain and fever	Ibuprofen superior to placebo for the relief of pain but only showed a trend toward being superior to acetaminophen
Bird (2007)[17]	N = 40 Ibuprofen 400 mg vs acetaminophen 650 mg in children 9–19 y old for control of pain after orthodontic separator placement	Ibuprofen and acetaminophen produced no significant differences in pain after separator placement
Bradley (2007)[22]	N = 187 Ibuprofen 400 mg twice a day vs acetaminophen 1000 mg twice a day in pts. 12–16 y old for treatment of orthodontic pain	Efficacy of ibuprofen superior to that of acetaminophen the day of surgery (orthodontic mean pain scores in favor of ibuprofen) but not on the following days
Clark (2007)[24]	N = 216 Ibuprofen 10 mg/kg vs acetaminophen 15 mg/kg vs codeine 1 mg/kg in children 6–17 y old for treatment of pain caused by musculoskeletal trauma	Ibuprofen more efficacious than acetaminophen, codeine, or placebo for pain relief due to musculoskeletal injuries
Derkay (1998)[31]	N = 136[a] Ibuprofen 10 mg/kg vs acetaminophen 10 mg/kg vs acetaminophen with codeine 10 mg/kg vs placebo in children for treatment of pain following myringotomy and tympanostomy	Although there was a trend toward ibuprofen and acetaminophen being more efficacious than codeine and placebo for pain, this difference was not statistically significant
Gazal (2007)[38]	N = 150 Ibuprofen 5 mg/kg vs acetaminophen 20 mg/kg vs acetaminophen 15 mg/kg vs acetaminophen 15 mg/ibuprofen 5 mg combination in children ages 2–12 y for treatment of pain following tooth extraction	Significant decreases in the mean pain scores with both ibuprofen alone and acetaminophen/ibuprofen combination compared to acetaminophen 15 mg/kg at 15 min postoperatively
Hamalainen (1997)[39]	N = 236[a] Ibuprofen 10 mg/kg vs acetaminophen 15 mg/kg vs placebo in children 4–15.8 y old for treatment of migreine headache	Ibuprofen more efficacious than acetaminophen or placebo for alleviation of headache
Hay (2008)[41]	N = 104 Ibuprofen 10 mg/kg up to 3 times/day vs acetaminophen 15 mg/kg up to 4 times/day in children 6 mo to 6 y of age for treatment of pain associated with illness	Neither ibuprofen nor acetaminophen was efficacious for the treatment of pain
Jackson (2006)[43]	N = 372[a] Ibuprofen 10 mg/kg 3 times/day vs acetaminophen 15 mg/kg 3 times/day vs placebo 3 times/day in children 4–6 y old for treatment of pain and fever caused by vaccination	Neither ibuprofen nor acetaminophen was more efficacious than placebo for the treatment of pain caused by vaccination
Kashefi (2005)[46]	N = 75[a] Ibuprofen 20 mg/kg vs acetaminophen 35 mg/kg vs placebo in children 3–12 y old for treatment of pain after lower abdominal surgery	Although ibuprofen and acetaminophen reduced postoperative agitation, neither reduced pain or rescue analgesic use compared to placebo
McGaw (1987)[55]	N = 123[a] Ibuprofen 200 mg vs acetaminophen 240 or 360 mg vs placebo in children 7–16 y old for control of pain after dental surgery	Efficacy of ibuprofen found to be superior to acetaminophen or placebo in the relief of postextraction pain
Moore (1985)[62]	N = 37[a] Ibuprofen 200 mg vs acetaminophen 240 or 360 mg vs acetaminophen 240 mg/codeine 24 mg vs placebo in children 5–12 y old for pain relief following dental extractions	Global rating of drug efficacy was statistically superior for ibuprofen; all 3 active agents were effective at 2 h
Primosch (1995)[69]	N = 60[a] Ibuprofen 150–300 mg vs acetaminophen 240–480 mg vs placebo in children 2–10 y old for pain relief following dental extraction	Although there was a trend toward reduced postextraction pain reported by parents of ibuprofen-treated pts., neither ibuprofen nor acetaminophen was statistically superior to placebo

Salmassian (2009)[72]	N = 60[a] Ibuprofen 400 mg 4 times/day on the first day and once daily on the following days vs acetaminophen 600 mg 4 times/day on the first day and once daily on the following days in children 12–18 y old for treatment of pain after orthodontic tooth movement	Neither ibuprofen nor acetaminophen was more efficacious than placebo for treatment of pain following orthodontic tooth movement
Schachtel (1993)[75]	N = 116[a] Ibuprofen 10 mg/kg vs acetaminophen 15 mg/kg vs placebo in children 2–12 y old for treatment of sore throat pain	Ibuprofen and acetaminophen rated superior to placebo for pain relief by both children and parents
Viitanen (2003)[84]	N = 119[a] Ibuprofen 15 mg/kg vs acetaminophen 40 mg/kg vs ibuprofen 15 mg/kg with acetaminophen 40 mg/kg combination vs placebo in children 1–6 y old for treatment of pain following adenoidectomy	Although the rate of hospital discharge was faster for pts. on ibuprofen than the other treatment groups, all treatments were identical in their ability to reduce pain

[a]N includes patients in the placebo group.

Table 3. Adult Temperature Reduction Data

Reference	Design and Dose	Overall Conclusion
Dippel (2003)[33]	N = 75[a] Ibuprofen 400 mg 6 times/day vs acetaminophen 1000 mg 6 times/day vs placebo 6 times/day in adults suffering acute ischemic stroke for efficacy in temperature maintenance/reduction	Neither ibuprofen nor acetaminophen more efficacious than placebo at reducing body temperature
Krishna (1995)[58]	N = 16 Ibuprofen 10 mg/kg vs acetaminophen 15 mg/kg in nonpregnant adults for treatment of malarial fever and headache	Ibuprofen more efficacious than acetaminophen in reducing fever through the first 4–5 h after medication
Leuschen (2004)[53]	N = 19 Ibuprofen 600 or 800 mg 3 times/day vs acetaminophen 1000 mg 4 times/day vs naproxen 400 mg twice/day in pts. 19–65 y old taking IFN beta-1a for MS for treatment of IFN-mediated adverse effects such as fever and headache	Ibuprofen and naproxen more efficacious than acetaminophen for reduction of fever associated with IFN beta-1a injection
Reess (2002)[70]	N = 104 Ibuprofen 400 mg 4 times/day vs acetaminophen 1000 mg 4 times/day in pts. taking IFN beta-1a for MS for treatment of IFN-mediated adverse effects of fever and headache	Both ibuprofen and acetaminophen equally efficacious in the relief of fever associated with interferon beta-1a injection
Rio (2004)[71]	N = 56 Ibuprofen 400 mg 3 times/day vs acetaminophen 500 mg 3 times/day vs prednisone 60 mg once a day in pts. ≥18 y old taking IFN beta-1a for MS for treatment of IFN-mediated adverse effects such as fever and headache	Ibuprofen and prednisone superior to acetaminophen for the relief of fever on the day of IFN beta-1a injection, but none of the treatments were efficacious on the days following the injection

IFN = interferon; MS = multiple sclerosis.
[a]N includes patients in the placebo group.

Table 4. Pediatric Fever Data

Reference	Design and Dose	Overall Conclusion
Aksoylar (1997)[7]	N = 151[a] Ibuprofen 8 mg/kg vs acetaminophen 15 mg/kg vs aspirin 15 mg/kg vs sponging in febrile children 6 mo to 5 y old for antipyretic efficacy	Ibuprofen and aspirin more efficacious for fever reduction (3 h after medication) than acetaminophen or sponging alone
Amdekar (1985)[8]	N = 39 Ibuprofen 7 mg/kg vs acetaminophen 8 mg/kg in febrile children 2–12 y old for antipyretic efficacy	Ibuprofen and acetaminophen equally efficacious at reducing the degree and duration of fever
Autret (1994)[10]	N = 154 Ibuprofen 7.5 mg/kg twice/day vs acetaminophen 10 mg/kg twice/day in febrile children 6 mo to 5 y old for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen at fever reduction over first 4 h after medication
Autret (1997)[11]	N = 228 Ibuprofen 7.5 mg/kg vs acetaminophen 10 mg/kg vs aspirin 10 mg/kg in febrile children aged 6–24 mo for analgesic and antipyretic efficacy and comfort	Overall efficacy of ibuprofen greater than that of aspirin or acetaminophen for reduction of fever, but acetaminophen had greater efficacy than ibuprofen for percentage of children with temp <38 °C 4 h after medication
Autret-Leca (2007)[12]	N = 301 Ibuprofen 10 mg/kg vs acetaminophen 15 mg/kg in febrile children 3 mo to 12 y old for antipyretic efficacy	Ibuprofen and acetaminophen equally efficacious at reducing fever
Bertin (1991)[15]	N = 231[a] Ibuprofen 10 mg/kg 3 times/day vs acetaminophen 10 mg/kg 3 times/day vs placebo 3 times/day in children 6–12 y old for treatment of sore throat pain and fever	Ibuprofen and acetaminophen equally more efficacious than placebo at fever reduction
Bertin (1996)[16]	N = 219[a] Ibuprofen 10 mg/kg 3 times/day vs acetaminophen 10 mg/kg 3 times/day vs placebo 3 times/day in children 1–6.75 y old for treatment of acute ear pain and fever	Ibuprofen more efficacious than placebo at fever reduction, but not more efficacious than acetaminophen
Figueras Nadal (2002)[34]	N = 187[a] Ibuprofen 6.67 mg/kg vs acetaminophen 10 mg/kg in febrile children (likely of infectious origin) 6 mo to 12 y old for antipyretic efficacy	Overall, ibuprofen and acetaminophen considered equally efficacious, but ibuprofen more efficacious at reducing temperature ≥2 °C
Hay (2008)[41]	N = 104 Ibuprofen 10 mg/kg up to 3 times/day vs acetaminophen 15 mg/kg up to 4 times/day in children 6 mo to 6 y old for treatment of fever due to illness	Ibuprofen more efficacious than acetaminophen for the treatment of fever caused by illness
Jackson (2006)[43]	N = 372[a] Ibuprofen 10 mg/kg 3 times/day vs acetaminophen 15 mg/kg 3 times/day vs placebo 3 times/day in children 4–6 y old for treatment of pain and fever caused by vaccination	Neither ibuprofen nor acetaminophen more efficacious than placebo for the treatment of fever caused by vaccination
Joshi (1990)[44]	N = 175 Ibuprofen 7 mg/kg vs acetaminophen 8 mg/kg in febrile children 4 mo to 12 y old for antipyretic efficacy	Overall, ibuprofen and acetaminophen considered equally efficacious, but acetaminophen was more efficacious at temperature reduction 30 min after medication
Kauffman (1992)[47]	N = 37[a] Ibuprofen 7.5 or 10 mg/kg vs acetaminophen 10 mg/kg vs placebo in febrile children 2–12 y old for antipyretic efficacy	Ibuprofen (both doses) more efficacious for fever reduction than acetaminophen or placebo
Kelley (1992)[48]	N = 36 Ibuprofen 6 mg/kg vs acetaminophen 10–15 mg/kg in febrile children 11 mo to 11.5 y old for antipyretic efficacy	Ibuprofen more efficacious for fever reduction than acetaminophen, but no difference in rescue medication requirement between treatment groups
Khubchandani (1995)[49]	N = 57 Ibuprofen 7 mg/kg vs acetaminophen 10 mg/kg vs mefenamic acid 6.5 mg/kg in young febrile children for antipyretic efficacy	Ibuprofen more efficacious for fever reduction than acetaminophen 2 and 3 h after medication, and mefenamic acid superior to both ibuprofen and acetaminophen
McIntyre (1996)[56]	N = 145 Ibuprofen 20 mg/kg/24 h vs acetaminophen 50 mg/kg/24 h in febrile children 2 mo to 12 y old for antipyretic efficacy	Ibuprofen and acetaminophen equally efficacious for fever reduction

Nwanyanwu (1999)[83]	N = 55 Ibuprofen 20 mg/kg/24 h vs acetaminophen 50 mg/kg/24 h in febrile children <5 y old for antipyretic efficacy	Ibuprofen and acetaminophen equally efficacious for fever reduction
Phadke (1985)[68]	N = 45 Ibuprofen 20 mg/kg 3 times/day vs age-dependent acetaminophen dose (62.5–250 mg) 3 times/day in young febrile children for antipyretic efficacy	Overall, ibuprofen and acetaminophen equally efficacious for fever reduction, but ibuprofen superior to acetaminophen for mean fall in temperature 1 h after dose
Schachtel (1993)[75]	N = 116[a] Ibuprofen 10 mg/kg vs acetaminophen 15 mg/kg vs placebo in febrile children 2–12 y old for antipyretic efficacy	Ibuprofen and acetaminophen equally more efficacious than placebo at reducing fever
Sheth (1980)[77]	N = 22 Calculated with Young's formula (based on ibuprofen 400 mg vs acetaminophen 300 mg) in febrile children 2–8 y old for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen at fever reduction 6 and 8 h after medication, and ibuprofen had a longer duration of action
Sidler (1990)[78]	N = 69 Ibuprofen 7 or 10 mg/kg vs acetaminophen 10 mg/kg in febrile children 5 mo to 13 y old for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen for fever reduction, as it had a faster onset of action and greater magnitude of temperature reduction, as well as lower mean temperatures and faster improvement of the clinical condition
Simila (1976)[79]	N = 48 Ibuprofen 0.5 or 6 mg/kg vs acetaminophen 12.5 mg/kg vs indomethacin 0.5 mg/kg vs aspirin 10 mg/kg vs aminophenazone 5 mg/kg in febrile children 3 mo to 13 y old for antipyretic efficacy	Ibuprofen showed a strong trend of being more efficacious at fever reduction than acetaminophen or aspirin and similar to that of aminophenazone, but indomethacin was superior to all treatment groups
Ulukol (1999)[80]	N = 60 Ibuprofen 10 mg/kg 3 times/day vs acetaminophen 10 mg/kg 3 times/day vs nimesulide 2.5 mg/kg 3 times/day in febrile children 2–14 y old for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen for fever reduction, but nimesulide superior to all treatment groups
Van Esch (1995)[81]	N = 70 Ibuprofen 5 mg/kg 4 times/day vs acetaminophen 10 mg/kg 4 times/day in febrile children 10 mo to 4 y old for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen for fever reduction
Vauzelle-Kervroedan (1997)[82]	N = 116 Ibuprofen ~10 mg/kg vs acetaminophen ~10 mg/kg in febrile children 0.67–11.92 y old for antipyretic efficacy	Ibuprofen and acetaminophen equally efficacious at reducing fever
Vinh (2004)[85]	N = 80 Ibuprofen 10 mg/kg 4 times/day vs acetaminophen 12 mg/kg 4 times/day in febrile children 2–14 y old for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen for fever reduction, especially for those of long duration
Walson (1989)[86]	N = 127[a] Ibuprofen 5 or 10 mg/kg vs acetaminophen 10 mg/kg vs placebo in febrile children 2–11 y old for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen and placebo at fever reduction 4, 6, and 8 h after medication and for the high-temperature group
Walson (1992)[87]	N = 61 Ibuprofen 2.5, 5, or 10 mg/kg 4 times/day vs acetaminophen 15 mg/kg 4 times/day in febrile children 6 mo to 11.6 y old for antipyretic efficacy	Ibuprofen and acetaminophen equally efficacious for fever reduction
Wilson (1984)[39]	N = 30 Ibuprofen 50, 100, or 200 mg (oral) 3 times/day vs acetaminophen 125, 250, or 500 mg (rectal) 3 times/day in febrile children 2–120 mo of age for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen for the magnitude and duration of fever reduction
Wilson (1991)[88]	N = 164[a] Ibuprofen 5 or 10 mg/kg vs acetaminophen 12.5 mg/kg vs placebo in febrile children 3 mo to 12 y old for antipyretic efficacy	Ibuprofen more efficacious than acetaminophen and placebo at fever reduction 4 h after medication and rate of reduction
Wong (2001)[90]	N = 419 Ibuprofen 5 or 10 mg/kg vs acetaminophen 12 mg/kg vs dipyrone 15 mg/kg in febrile children 6 mo to 6 y old for antipyretic efficacy	Ibuprofen and dipyrone more efficacious than acetaminophen at fever reduction 3, 4, 5, and 6 h after medication and in the number of pts. who achieved temperatures ≤37.5 °C

[a]N includes patients in the placebo group.

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Eficacia y Seguridad de Ibuprofén y Acetaminofén en Niños y Adultos: Meta Análisis y Revisión Cualitativa

CA Pierce y B Voss

Ann Pharmacother 2010;44:489-506.

EXTRACTO

OBJETIVO: Evaluar la eficacia y seguridad analgésica y antipirética de ibuprofén y acetaminofén en niños y adultos

FUENTES DE INFORMACIÓN: Se realizó una búsqueda de la literatura en los sistemas PubMed/MEDLINE y EMBASE utilizando los términos ibuprofén y acetaminofén. Para esta revisión fueron elegibles sólo los artículos que compararon directamente ibuprofén con acetaminofén.

SÍNTESIS: Se identificaron 85 estudios, los cuales compararon directamente ibuprofén con acetaminofén: 54 contenían datos de eficacia analgésica, 35 contenían datos en la reducción de temperatura/antipirético, y 66 contenían datos de seguridad (nota: algunos artículos contenían datos de analgesia y/o antipirético y/o seguridad). La revisión cualitativa reveló que ibuprofén fue más eficaz que acetaminofén, en la mayoría de la literatura evaluada en esta revisión, para el tratamiento de dolor y fiebre en ambas poblaciones de pacientes, pediátricos y adultos y que los mismos fueron igualmente seguros. Los meta-análisis de los subgrupos de estudios clínicos aleatorios que reportaron suficiente información cuantitativa para calcular tanto la razón de probabilidad (odds ratio) (eventos adversos) como la diferencia en el promedio estandarizada (dolor y fiebre), confirmó los resultados cualitativos de dolor para adulto (diferencia en promedio estandarizada de 0.69; 95% CI 0.57 y 0.81) y pediátrico (diferencia en promedio estandarizada de 0.28; 95% CI 0.10 y 0.46) a las 2 horas luego de la dosis y fiebre pediátrica (diferencia en promedio estandarizada de 0.26; 95% CI 0.10 y 0.41) a las 4 horas luego de la dosis. Conclusiones relacionadas a la reducción en temperatura/fiebre en adultos no se pudieron realizar debido a la falta de datos evaluables. La razón de probabilidad combinada para la proporción de sujetos adultos que experimentaron al menos un evento adverso, favoreció levemente a ibuprofén; sin embargo, la diferencia no fue estadísticamente significativa (1.12; 95% CI 1.00 y 1.25). No se encontró diferencia en la incidencia de eventos adversos en pacientes pediátricos (0.82; 95% CI 0.60 y 1.12).

CONCLUSIONES: Ibuprofén es tan o más eficaz que acetaminofén para el tratamiento del dolor y fiebre en poblaciones adultas y pediátricas e igualmente seguro.

Traducido por Jennifer Guzmán

Efficacité et Sécurité de l'Ibuprofène et de l'Acétaminophène chez les Enfants et les Adultes: Méta-Analyse et Revue Qualitative

CA Pierce et B Voss

Ann Pharmacother 2010;44:489-506.

RÉSUMÉ

SOURCES DE L'INFORMATION: PubMed/MedLINE, et EMBASE, et les articles tirés des bibliographies.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Les recherches sur les bases de données PubMed/MedLINE, et EMBASE ont été réalisées avec les mots-clés ibuprofen et acetaminophen. Seuls les articles qui comparaient directement l'ibuprofène et l'acétaminophène étaient éligibles pour cette révision.

SYNTHÈSE DE L'INFORMATION: Quatre-vingt cinq études comparant directement l'ibuprofène et l'acétaminophène ont été identifiées; 54 contenaient des données sur l'efficacité analgésique, 35 contenaient des données sur l'efficacité antipyrétique, et 66 contenaient des données sur la sécurité (note: certains articles contenaient des données sur l'efficacité analgésique et/ou antipyrétique et/ou la sécurité.) La révision qualitative a révélé que l'ibuprofène est plus efficace que l'acétaminophène dans la plupart des études évaluées dans le traitement de la douleur et de la fièvre, et ce, tant au sein de la population pédiatrique qu'adulte. Cette révision démontre aussi que les 2 médicaments sont également sécuritaires. La méta-analyse réalisée avec le sous-groupe d'études cliniques qui rapportaient suffisamment d'informations quantitatives pour calculer un rapport de cote (réactions indésirables) ou une différence moyenne standardisée (douleur et fièvre), vient confirmer les résultats de l'analyse quantitative chez les adultes (différence moyenne standardisée 0.69; IC 95% 0.57 à 0 81), et chez les enfants (différence moyenne standardisée 0.28, IC 95% 0.10 à 0.46) pour la douleur 2 heures post dose et pour la fièvre en pédiatrie (différence moyenne standardisée 0.26; IC 95% 0.10 à 0.41) 4 heures post dose. Il a été impossible de tirer des conclusions concernant la réduction de la fièvre/température chez les adultes en raison de l'absence de données. Les rapports de cote combinés pour la proportion de sujets adultes qui ont présenté au moins un épisode de réaction indésirable favorise légèrement l'ibuprofène; cependant, cette différence n'était pas statistiquement significative (1.12; IC 95% 1 00 à 1.5). Aucune différence n'a été notée dans la population pédiatrique concernant l'incidence d'effets indésirables (0.82; IC 95% 0.60 à 1.12)

CONCLUSIONS: L'ibuprofène est au moins aussi efficace que l'acétaminophène pour le traitement de la douleur ou de la fièvre chez les adultes ou les enfants et semble tout aussi sécuritaire.

Traduit par Marc Parent

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Papers

Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis

David Henry, *senior lecturer in clinical pharmacology*,[a] **Lynette L-Y Lim**, *senior lecturer in biostatistics*,[a] **Luis A Garcia Rodriguez**, *director*,[b] **Susanne Perez Gutthann**, *head of pharmacoepidemiology research*,[c] **Jeffrey L Carson**, *professor and chief*,[d] **Marie Griffin**, *associate professor in medicine and preventive medicine*,[e] **Ruth Savage**, *general practitioner*,[f] **Richard Logan**, *reader in clinical epidemiology*,[g] **Yola Moride**, *assistant professor*,[h] **Chris Hawkey**, *professor of gastroenterology*,[i] **Suzanne Hill**, *acting head, drug safety, evaluation board*,[j] **James T Fries**, *professor of medicine*

[a] Centre for Clinical Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, University of Newcastle, New South Wales, Australia, [b] Centro Espanol de Investigacion, Farmacoepidemiologica, Universidad Complutense de Madrid, 28040 Madrid, Spain, [c] Pharmacoepidemiology Research, Ciba-Geigy SA, Medical Department, 08013 Barcelona, Spain, [d] Division of General Internal Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ 08903, USA, [e] Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, TN 37232, USA, [f] Department of Rheumatology, Christchurch Hospital, Christchurch, New Zealand, [g] Department of Public Health and Epidemiology, University of Nottingham Medical School, Queen's Medical Centre, Nottingham NG7 2UH, [h] Centre for Clinical Epidemiology and Community Studies, McGill University-Jewish General Hospital, Montreal, Quebec H3T 1E2, Canada, [i] Division of Gastroenterology, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, [j] Therapeutics Goods Administration, Department of Human Services and Health, PO Box 100, Woden, ACT 2606, Australia, [k] Stanford University School of Medicine, Suite 203, Palo Alto, CA 94304-1808, USA

Abstract

Objective: To compare the relative risks of serious gastrointestinal complications reported with individual non-steroidal anti-inflammatory drugs.
Design: Systematic review of controlled epidemiological studies that found a relation between use of the drugs and admission to hospital for haemorrhage or perforation.
Setting: Hospital and community based casecontrol and cohort studies.
Main outcome measures: (a) Estimated relative risks of gastrointestinal complications with use of individual drugs, exposure to ibuprofen being used as reference; (b) a ranking that best summarised the sequence of relative risks observed in the studies.
Results: 12 studies met the inclusion criteria. 11 provided comparative data on ibuprofen and other drugs. Ibuprofen ranked lowest or equal lowest for risk in 10 of the 11 studies. Pooled relative risks calculated with exposure to ibuprofen used as reference were all significantly greater than 1.0 (interval of point estimates 1.6 to 9.2). Overall, ibuprofen was associated with the lowest relative risk, followed by diclofenac. Azapropazone, tolmetin, ketoprofen, and piroxicam ranked highest for risk and indomethacin, naproxen, sulindac, and aspirin occupied intermediate positions. Higher doses of ibuprofen were associated with relative risks similar to those with naproxen and indomethacin.
Conclusions: The low risk of serious gastrointestinal complications with ibuprofen seems to be attributable mainly to the low doses of the drug used in clinical practice. In higher doses ibuprofen is associated with a similar risk to other non-steroidal anti-inflammatory drugs. Use of low risk drugs in low dosage as first line treatment would substantially reduce the morbidity and mortality due to serious gastrointestinal toxicity from these drugs.

Key messages

- Because there are no important differences in efficacy, choice of first line treatment with these drugs should be based on their relative toxicity
- Meta-analysis of the available epidemiological studies shows wide differences between individual drugs in the risk of inducing gastrointestinal bleed- ing and ulcer perforation
- Of the drugs in common use, ibuprofen and diclofenac rank low in toxicity whereas azapropa- zone, ketoprofen, and piroxicam rank high
- Some of the differences between drugs may be explained by dose, and the advantage of "low risk" drugs may be lost once their dose is increased

Introduction

Interventions to reduce the morbidity and mortality from upper gastrointestinal disease caused by the widespread use of non-steroidal anti-inflammatory drugs include educational methods aimed at reducing prescribing, coprescription of a mucosal protective drug such as misoprostol, and the use of paracetamol as an alternative analgesic.[1,2] Another approach is to prescribe a drug associated with a comparatively low risk of gastrointestinal toxicity and use more toxic compounds only in the event of a poor clinical response to the first line drug.[3,4] However, evaluation of the data on comparative risk is difficult. Published epidemiological studies have provided variable coverage of individual drugs, making them unsuitable for meta-analytical approaches that attempt to pool data across all studies.[3] Also, apparent differences in the risks of gastrointestinal complications could be due to factors such as variation in the doses used or differences in the age or susceptibilities of the recipients of the various drugs.

We used meta-analytical methods to explore the range of reported relative risks. We were interested in the extent to which differences between drugs could be explained by the doses used. Our main hypothesis was that ibuprofen in the doses used in practice is associated with a lower relative risk of major upper gastrointestinal complications than other members of the class.[3,4]

Methods

LITERATURE SEARCH

A search of Medline CD-ROM was conducted for 1985-94 inclusive. This was supplemented by a review of the bibliographies of previously published meta-analyses and reviews.[5,6] Authors of relevant studies were contacted and asked to update their published results. In addition, they were sent a list of studies and asked whether they knew of work that was not listed.

QUALITY ASSESSMENT

We identified controlled epidemiological studies that found a relation between the use of non-steroidal anti-inflammatory drugs in the community and the development of serious peptic ulcer complications necessitating admission to hospital.[3,7,8,9,10,11,12,13,14,15,16,17,18] Some studies did not provide data on the use of individual drugs or did not show the association with gastrointestinal damage. These studies were excluded from further consideration. The remaining studies were assessed by the following criteria: ascertainment and validation of study outcomes, selection and comparability of controls, ascertainment of exposure, and control or adjustment for potential confounders. Tables summarising the results of these

assessments and a list of excluded studies, with reasons for their rejection, are available by writing direct to DH.

DATA EXTRACTION

Data were extracted by LL and DH, differences being resolved by consensus. We extracted both the adjusted relative risks when these were provided by authors and the raw data relating to the use of individual drugs by cases and controls. These tasks were completed after a workshop attended by representatives of some of the groups that had carried out relevant studies. At the workshop authors clarified certain points and provided further data from three published studies, a reanalysis and extension of a previous study, and data on one unpublished study.[7 10 13 15 16 17]

STATISTICAL METHODS

In estimating pooled relative risks we included only studies that provided comparative data for ibuprofen and the other drugs of interest. Consequently, the numbers of studies that contributed to the analyses varied from drug to drug. We calculated for every study the estimated relative risk of gastrointestinal complications with each comparator drug, exposure to ibuprofen rather than non-use of a drug being taken as reference. The odds ratio was assumed to provide a valid estimate of the relative risk. This required reanalysis of raw data from the authors' tables. It was necessary for some authors to provide unpublished data to enable this analysis to be carried out.[7 10 14 15 16 17] These data did not include adjustments for potential confounders. The estimated relative risks were pooled across studies by using the random effects model of Der Simonian and Laird.[19]

FINDING A SUMMARY RANK OF RELATIVE RISKS WITH INDIVIDUAL DRUGS

We tried to find an order that best summarised the sequence of adjusted relative risks seen with the drugs that had been included in two or more studies. The main advantage of this approach was that it maintained the within study comparisons and implicitly compared each agent simultaneously with every other drug analysed in a particular study.

The method entailed comparing all possible orderings of the non-steroidal anti-inflammatory drugs with the actual rankings observed in the studies. (We use the term ordering to refer to any theoretically possible arrangement of the drugs with respect to risk of complications and the term ranking to refer to the arrangements of the drugs observed within the studies.) A score was assigned to each of the 12 factorial possible orderings of the 12 drugs that were included in two or more studies. The score was derived as follows. The ranking of drugs by their relative risks in each study was compared with a given ordering in a pairwise fashion, the arrangement of each pair of agents in the study ranking being compared with that of the corresponding pair in the ordering, and a partial score allocated. Hence for a study with n drugs there was a total of n(n - 1)/2 partial scores.

Partial scores were defined to take values between -1.0 and 1.0.A score was negative if the arrangement of the comparison pair in the study ranking was the opposite of that in the ordering being considered and positive otherwise. As a measure of the difference in risk between the pair of drugs we calculated a P value by statistical testing of the difference in relative risk between the two drugs. The partial score was calculated as 1.0 minus the P value, so that when the P value was small the partial score was close to 1.0 (thus making a large relative contribution to the score). When the P value was large the partial score was close to zero. With a relation of this nature, small studies contributed little because partial scores were small owing to their large P values. The total score associated with a particular ordering was the sum of the partial scores across all 12 studies (see below). The ordering associated with the maximum score was defined as the "best."

ASSESSING DOSE EFFECTS WITH INDIVIDUAL DRUGS

To evaluate dose effects with individual drugs we pooled the adjusted relative risks in strata defined by the dosage cut points reported by the authors. Five studies contributed data to the analyses of ibuprofen and naproxen[3 10 14 15 18] and three to the analysis of indomethacin.[10 15 18] The daily dosage cut points for each drug varied from study to study as follows: ibuprofen 1200 mg,[3 14] 1500 mg,[15 18] and 2400 mg[10]; naproxen 500 mg,[3] 750 mg,[15 18] and 1000 mg[10 14]; and indomethacin 75 mg[15 18] and 100 mg.[10] Relative risks for doses below the cut points were assigned to the low dose stratum and those above the cut points assigned to the high dose stratum. Within strata relative risks were pooled by the random effects model.[19]

Results

We identified 12 studies that examined relative risks of gastrointestinal complications with a total of 14 nonsteroidal anti-inflammatory drugs and satisfied our criteria for inclusion. Twelve drugs had been included in two or more studies and 11 studies provided comparative data on ibuprofen and other agents.[3 7 8 9 10 11 12 13 14 15 16 17 18] Two reports were unpublished at the time of writing: one was an update and reanalysis of a previously published paper; the other had been published only as an abstract.[15 17] Three other studies were updated by the authors at the investigators' workshop or in subsequent correspondence.[7 10 14] All but one paper described casecontrol studies; three of the 12 used linkage of administrative records and one used computerised medical records. Three studies that employed automated records included validation of original medical records to ensure that patients had experienced the outcomes of interest.[10 15 18] However, one early study relied entirely on recorded diagnoses.[9]

All of the ad hoc studies employed classic case finding techniques with diagnostic confirmation of case status and ascertainment of prior drug use by structured interview. Controls in these studies were recruited from the community or from the same hospitals as the cases. Time windows for exposure also varied across the studies (from one week to three months). The most common exposure period was one week.

Despite variations in design and conduct of the studies the overall results were closely similar. When the estimated overall relative risks of complications with the use of non-steroidal anti-inflammatory drugs were calculated they lay mainly in the interval 3.0-5.0. These results were consistent with the findings of other meta-analyses.[5 6] Full details of these studies, including tables of overall results and data on the influence of dose, duration of treatment, and age and sex of recipients, are available on request.

RELATIVE RISKS WITH INDIVIDUAL DRUGS

Figure 1 shows the point estimates for the relative risks of serious gastrointestinal complications with the individual drugs. There was a wide distribution of results but figure 1 suggests that true differences existed between the drugs.

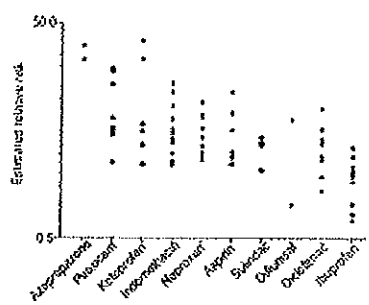

Fig 1--Estimated relative risks of major gastrointestinal complications with individual non-steroidal anti-inflammatory drugs (calculated with non-use of non-steroidal anti-inflammatory drugs as reference)

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Table 1 gives the pooled relative risks for individual agents calculated with exposure to ibuprofen as reference. The different numbers of studies that contributed to the analyses reflected their variable coverage of individual drugs. In each case the relative risk with exposure to the comparator compared with exposure to ibuprofen was significantly greater than 1.0. Table 1 shows that the comparator drugs were associated with a 1.6-fold to 9.2-fold increase in the risk of serious upper gastrointestinal complications compared with ibuprofen. These analyses included no adjustments for potential confounding factors as they were based on the authors' raw data.

Table 1--Comparison of comparative toxicity of range of drugs with use of ibuprofen as reference for calculating relative risks

Comparator	No of studies	Pooled relative risk	95% Confidence interval for pooled relative risk	P value (heterogeneity)
Ibuprofen	--	1.0+	--+	--+
Fenoprofen	2	1.6	1.0 to 2.5	0.310
Aspirin	6	1.6	1.3 to 2.0	0.685
Diclofenac	8	1.8	1.4 to 2.3	0.778
Sulindac	5	2.1	1.6 to 2.7	0.685
Diflunisal	2	2.2	1.2 to 4.1	0.351
Naproxen	10	2.2	1.7 to 2.9	0.131
Indomethacin	11	2.4	1.9 to 3.1	0.488
Tolmetin	2	3.0	1.8 to 4.9	0.298
Piroxicam	10	3.8	2.7 to 5.2	0.087
Ketoprofen	7	4.2	2.7 to 6.4	0.258
Azapropazone	2	9.2	4.0 to 21.0	0.832

+ Reference category for calculating relative risk.

Table 2 lists the rankings achieved by individual drugs in the 12 studies. Ibuprofen was associated with the lowest relative risk (highest rank) in nine studies and equal lowest relative risk in one study. Several other drugs showed considerable variation in ranking among studies.

Table 2--Within study rankings of drugs according to relative risks of major gastrointestinal complications

Reference	Ibuprofen	Diclofenac	Diflunisal	Fenoprofen	Aspirin	Sulindac	Naproxen	Indomethacin	Piroxicam	Ketoprofen	Tolmetin	Azapropazone
Somerville et al (1986)[2]	1	--	--	--	3	--	2	4	5	--	--	--
Carson et al (1987)[9]	1.5	--	--	1.5	--	6	4	3	--	--	5	--
Laporte et al (1991)[11]	--	4	--	--	3	--	2	1	5	--	--	--
Griffin et al (1991)[10]	1	--	--	4.5	--	3	4.5	2	6	--	8	--
Nobili et al (1992)[13]	2.5	4	--	--	6	--	2.5	5	1	--	--	--
Savage et al (1993)[12]	1	4	--	--	3	5	6	8	7	2	--	--
Kaufman et al (1993)[14]	1	2	--	--	4	--	5	3	6	7	--	--
Henry et al (1993)[7]	1	3	2	--	5	4	7	6	9	8	--	--
Garcia Rodriguez and Jick (1994)[15]	1	3	--	--	--	--	2	5	6	4	--	7
Langman et al (1994)[1]	1	3	--	--	2	--	4	5	6	7	--	8
Abenhaim and Moride[17]	1	2	--	--	--	--	4	3	6	5	--	--
Perez Gutthann et al (1994)[18]	1	3	8	--	--	--	4	3	5	7	--	--
No of studies	11	9	2	2	7	5	12	12	11	7	2	2

Table 3 gives the summary statistics obtained with the ranking method. Drugs that appeared in two or more studies were included in the analysis to obtain a weighted summary order according to relative risk. Twelve orderings achieved equal highest score. Ibuprofen ranked lowest, followed by diclofenac; data for the other drugs are summarised in table 3. An idea of the stability of the position of each drug in the 12 top scoring orderings can be obtained by comparing its highest and lowest values. Values for fenoprofen seemed unstable, probably because it was included in only two studies. The positions of the remaining

drugs seemed fairly stable, though data for diflunisal, tolmetin, and azapropazone must be treated with caution owing to the small numbers of contributing studies.

Table 3--Results obtained with summary ranking method

	Summary statistics obtained with ranking method+			
Comparator	Mean rank	SD	Minimum rank	Maximum rank
Ibuprofen	1.0	0	1	1
Diclofenac	2.3	0.5	2	3
Diflunisal	3.5	0.5	3	4
Fenoprofen	3.5	1.2	2	5
Aspirin	4.8	0.5	4	5
Sulindac	6.0	0	6	6
Naproxen	7.0	0	7	7
Indomethacin	8.0	0	8	8
Piroxicam	9.0	0	9	9
Ketoprofen	10.3	0.5	10	11
Tolmetin	11.0	0.9	10	12
Azapropazone	11.7	0.5	11	12

+ Analysis based on 12 orderings that achieved equal highest score.

IMPORTANCE OF DOSE

Data on the distribution of relative risks according to dose of the individual drugs were available from five studies. Sample sizes were small, effectively limiting comparisons to the commonly used drugs. Extractable comparative data were available from the five studies relating to ibuprofen, naproxen, and indomethacin. By using the arbitrary dose stratifications chosen by the authors (see above) the following pooled relative risks were obtained: low dose--ibuprofen 1.6 (95% confidence interval 0.8 to 3.2), naproxen 3.7 (1.7 to 7.7), and indomethacin 3.0 (2.2 to 4.2); high dose--ibuprofen 4.2 (1.8 to 9.8), naproxen 6.0 (3.0 to 12.2), and indomethacin 7.0 (4.4 to 11.2).

Discussion

This meta-analysis suggests that ibuprofen, as used in clinical practice in seven countries, was associated with the lowest relative risk of severe gastrointestinal toxicity of the 12 non-steroidal anti-inflammatory drugs investigated in two or more studies. The differences seemed to be attributable to the fairly low dose of ibuprofen employed in clinical practice. We could find no evidence that the lower relative risk with ibuprofen was due to differences in the characteristics of the recipients of the different drugs that might have led to altered susceptibility to their gastrointestinal effects (data not shown).

Langman et al highlighted the possible advantages of ibuprofen. They concluded that meta-analysis was difficult because comparable datasets could not be extracted from the available studies.[3] Our analytical approach restricted analyses to studies that had collected data relevant to the comparisons of interest. Our conclusions about the apparent advantage of ibuprofen were unchanged whether our analyses were based on pooling of unadjusted relative risks calculated from the raw data (ibuprofen being used as reference) or an alternative approach in which we tried to find an order that best summarised the rankings (by adjusted relative risk) seen in the individual studies. The summary ranking procedure has the advantage that it

compares each drug with every other. Of the commonly used agents, ibuprofen and diclofenac ranked lowest by relative risk, ketoprofen and piroxicam ranked highest, and aspirin, sulindac, naproxen, and indomethacin held the middle rankings. Diflunisal, fenoprofen, and tolmetin were not included in enough studies for confident conclusions to be drawn about their relative toxicities. Azapropazone was included in two studies, both from the United Kingdom, but the relative risk estimates were so high that there must be doubt about its suitability for routine use.

IMPORTANCE OF DOSE

Five studies provided data on relative risk stratified by the dose of individual drugs consumed before the index day.[3 10 14 15 18] Pooling of these studies yielded positive dose-response relations for ibuprofen, naproxen, and indomethacin. Confidence intervals for the pooled relative risks with low doses of these drugs overlapped, as did the values for higher doses. The most likely explanation for the low overall relative risk seen with ibuprofen in the main analyses is that in practice it is used in comparatively lower doses than the other drugs reviewed. It should not be assumed that the apparent advantage of ibuprofen persists when doses are increased beyond 1600 mg daily. The evidence reviewed indicates that it does not.

Arguably if the low risk seen with ibuprofen (and diclofenac) is attributable simply to dose, then this does not represent a true advantage. However, the risks recorded in these studies were associated with the doses of ibuprofen and diclofenac actually used in populations around the world. It is likely that these doses were associated with clinical benefit.

Clinical and regulatory decisions have to be made on the basis of the data reviewed here. Though there have been calls for the withdrawal of piroxicam,[20] we do not support this approach. There is considerable variability in the clinical responses to different agents, and withdrawal of particular agents may deny treatment to patients in whom the benefits outweigh the risks. Our preference is to inform doctors and the public of the apparent advantages and disadvantages of the various non-steroidal anti-inflammatory drugs and to encourage use of the lowest effective doses of drugs that seem to be associated with a comparatively low risk. Progression to higher doses or switching to drugs that are associated with higher risks should occur only when the clinical situation requires it and after consideration of the benefits and risks to the patient concerned. On the basis of the data reviewed, use of regimens with comparatively low risks of gastrointestinal complications could result in substantial reductions in morbidity and mortality.

A full version of this meta-analysis may be obtained by writing direct to DH. We acknowledge the support of Boots Australia Pty Ltd, which funded an investigators' workshop in Newcastle, Australia, on 23 and 24 September 1993.

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Conflict of interest: None.

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NPS NEWS
National Prescribing Service Newsletter
2
ISSN 1441-7421 FEB 99

Before prescribing NSAIDs, consider

N Non-drug treatment
physiotherapy, exercise or rest, weight reduction

S Simple analgesics
eg paracetamol

A Adverse effects of NSAIDs
eg reduced renal function, gastric bleeding and implications for other conditions eg heart failure

I Interacting medications
eg ACE inhibitors, corticosteroids, cyclosporin, diuretics, lithium, methotrexate, potassium supplements, potassium sparing diuretics, and warfarin

Informing patient about:
signs of adverse effects of NSAIDs (eg dark stools, swollen ankles, heartburn or indigestion), avoiding over the counter aspirin and NSAIDs, proposed dosing strategy and use of paracetamol

D Drugs
choose lower risk, short acting agents (ibuprofen or diclofenac) first

Dose
as low and infrequent as possible

S Suspect
new symptoms may be due to adverse effects

Stop medication as soon as possible

What should I take for the pain, doctor?

In this issue we review current information on the role of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in managing pain to assist you in choosing the right treatment for your patients.

In addition to receiving the safest, most effective treatment, it is important that patients understand the cause of their pain and are encouraged to return to you if the treatment is not working.

Wise use of NSAIDs

NSAIDs have analgesic, anti-inflammatory and antipyretic effects.

NSAIDs are particularly useful in the symptomatic treatment of conditions where prostaglandin production / inflammation is prominent, for example:

- dysmenorrhoea
- metastatic bone pain
- inflammatory arthropathies (eg rheumatoid arthritis, ankylosing spondylitis, Reiters syndrome)
- acute gout.

Where inflammation is less prominent, NSAIDs are less likely to offer additional benefit over simple analgesics.

Consider simple analgesic/non-drug measures as first line therapy in the following:

- headache
- osteoarthritis
- strains and sprains
- mechanical back pain
- tendinitis (eg supraspinatus, Achilles)
- enthesopathies (eg tennis elbow, plantar fasciitis).

Consider the risks

NSAIDs are not without risks; their use requires careful risk/benefit assessment.

Gastrointestinal bleeding or perforation – the major risk. The risk is increased in older patients and in those with a history of gastrointestinal disease. Use of higher doses and longer duration also increase the risk.[1]

Renal failure – in patients with reduced renal blood flow, NSAIDs can precipitate renal failure.

Heart failure – NSAIDs cause salt and water retention and may exacerbate or precipitate congestive heart failure in susceptible patients (eg elderly patients taking diuretics).

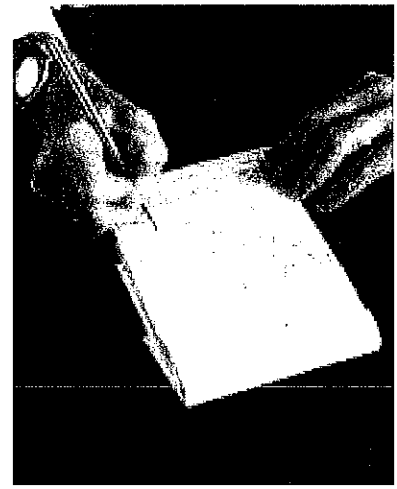
Bronchospasm – may occur with NSAIDs and/or aspirin in sensitive people.

Elevated blood pressure – a recent meta-analysis found the magnitude of effect to be 5mm Hg.[2]

Dyspepsia, nausea, headache and fluid retention – are common.

Hypersensitivity reactions, eg angioedema – occur rarely.

Blood dyscrasias – occur rarely.



The National Prescribing Service (NPS)

Supporting quality prescribing in Australia

The NPS grew out of a need for doctors and other prescribers to have access to a range of coordinated activities relating to quality prescribing.

Before setting up the NPS, three rounds of consultation were conducted with more than 1,400 people around Australia including doctors, pharmacists, consumers and other health professionals. More than 60 divisions of general practice participated in the consultation process.

The consultation recommended that the NPS:

- coordinate and facilitate effective quality prescribing initiatives
- provide quality prescribing information and feedback
- develop quality prescribing policy
- evaluate prescribing strategies.

The NPS has commenced its program of providing feedback on prescribing to all GPs around Australia, and independent information to all prescribers via NPS News. Negotiations are currently proceeding with divisions of general practice who have indicated an interest in implementing NPS programs with and for local GPs.

The NPS is independent of government intervention and is not part of the pharmaceutical industry.

For further information, phone (02) 9332 3944.

Your views on *Case Study 1*

We were overwhelmed with responses to the case study in NPS News 1: Mr Smith the 43 year old taxi driver.

Here is a snapshop of the aggregated responses:

- 42% of doctors said they would refer Mr Smith for endoscopy and biopsy
- 22% said they would do a H.pylori breath test
- 46% prescribed ranitidine, usually for a limited period
- 37% chose to write no prescription, awaiting test results or recommending lifestyle measures first. A range of advice was offered to tbe patient about smoking, alcohol consumption, diet and exercise.

Unusual prescriptions included ranitidine and nizatadine together; ranitidine and omeprazole together; 'tds' ranitidine. The rationale for these prescriptions is questionable. A full summary of responses has been sent to all doctors who sent in the case study.

In this issue *References*

What should I take for the pain, doctor?

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Contributing authors

Ms Eve Hurley BPharm (Hons)
Senior Editor, Australian Medicines Handbook

Ms Anna Drew BPharm (Hons)
Director, Hunter Drug Information Service

Reviewers

Prof Peter Brooks, Dean, Faculty of Medicine, University of Queensland

Dr Nick Carr, general practitioner

Ms Jan Donovan, consumer

Dr John Dowden, Australian Prescriber

Ms Mary Hemming, Therapeutic Guidelines Ltd

Prof David Henry, Professor of Clinical Pharmacology, University of Newcastle

Dr Peter Keppel, general practitioner

Prof John Murtagh, Royal Australian College of General Practitioners

Ms Susan Parker, Astra Pharmaceuticals Pty Ltd

Ms Simone Rossi, Australian Medicines Handbook

NPS

National Prescribing Service Limited

Our goal To improve health outcomes for Australians through prescribing that is: • safe • effective • cost-effective. **Our programs** To enable prescribers to make the best prescribing decisions for their patients, the NPS provides • information • education • support and other resources.

9 Leichhardt St Darlinghurst NSW 2010

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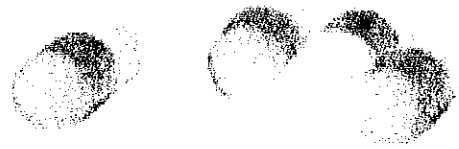
Thank you to all those doctors who provided feedback on the first NPS Prescribing Practice Review on H. pylori. All GPs will soon be mailed more specific information on NSAIDs in our next Prescribing Practice Review.



Prescribing pointers

If NSAIDs are indicated, which should be used?

Before prescribing an NSAID, consider differences in:

Efficacy

- Differences in anti-inflammatory activity between agents is small when compared with inter-patient differences in response and adverse effects.
- About 60% of patients[1] will respond to any NSAID particularly when arthralgia is the primary complaint.[2]
- If one NSAID is not successful (after two weeks at appropriate dose) the patient may respond to another NSAID.

Safety

- A meta-analysis[3] showed the following differences between individual drugs in the risk of inducing gastrointestinal bleeding and ulcer perforation:
  - ❑ lowest pooled relative risk: ibuprofen (when used at doses of less than 1600mg per day) and diclofenac
  - ❑ highest pooled relative risk: piroxicam and ketoprofen.

  Some of the differences in relative risk between drugs may be due to dose; benefit of lower risk may be lost once dose is increased.
- Central nervous system adverse effects (eg headache, vertigo) are common with indomethacin.
- Cystitis can occur with tiaprofenic acid.
- Enteric coating or suppository formulations have little effect on the incidence of ulceration or bleeding but may reduce dyspepsia. To reduce the risk of dyspepsia, NSAIDs should be given with food.

Convenience

Long-acting agents or formulations are useful for patients with chronic inflammatory disease and night-time pain or morning stiffness.

There is little difference in anti-inflammatory activity between NSAIDs. Choice of NSAID should be made on relative gastrointestinal toxicity, duration of action, patient response and tolerance.

A Complementary *Update*

A number of herbs are recommended to patients for anti-inflammatory effects although surveys suggest they are not always useful.

Herbs used include ginger, celery, Devil's claw, willow bark, guaiacum, black cohosh, chamomiles, prickly ash bark, golden rod, sawpalmetto, Butcher's broom, comfrey and glycyrrhiza species.

A concentrated extract of ginger *(Zingiber officinale)* is found in Zinax® which has been promoted for temporary relief of arthritic symptoms.

Supporting evidence for this particular use of ginger is felt to be insufficient. Results in seven rheumatoid patients taking 5-15g/day fresh ginger or 0.5-1g/day dried ginger for three months prompted a survey of interested patients taking ginger.[1]

Responses from 28 subjects with rheumatoid arthritis, 18 with osteoarthritis and 10 with muscular discomfort iudicated that more than 75% of arthritis patients and all those with muscular discomfort reported relief from pain and swelling. Benefit is postulated to result from dual inhibition of lipo-oxygeuase and cyclo-oxygenase pathways.

Relief of muscle and joint pain was reported by 25 of 28 polyarthritis patients participating in an open dose-finding study for Zinax®.

A controlled, double blind, crossover trial in 56 osteoarthritis patients showed that Zinax® performed slightly better than placebo and disappointingly compared to ibuprofen on a visual analogue scale of pain and reduction in rescue acetylsalicylate requirements.[2] The formulation has since been changed and published results of a larger study are expected soon.

Adverse effects experienced with ginger include difficulty in tolerating the strong taste and gastrointestinal symptoms. The toxicology of concentrated products is unknown.

For further information on NSAIDs see:

Therapeutic Guidelines: Analgesic, 3rd Edition, Therapeutic Guidelines Limited, Victoria, March 1997.
Therapeutic Guidelines: Gastrointestinal, 2nd Edition, Therapeutic Guidelines Limited, Victoria, August 1998.
Australian Medicines Handbook, Australian Medicines Handbook, South Australia, 1998.

GP Exchange

a column in which GPs share their prescribing experiences

Patient: A 76 year old woman with a long history of severe osteoarthritis who complained of increasing urinary problems, with frequency, irritation and nocturia

Current medication: Daily NSAID, tiaprofenic acid (Surgam®)

Scenario: Several MSUs showed lots of cells but no infection. The woman had marked atrophic vaginitis but despite first local oestrogen creams and then hormone replacement therapy her symptoms persisted.

Diagnosis: Eventually cystoscopy revealed gross cystitis, presumed secondary to her daily NSAID, tiaprofenic acid (Surgam®). Rare side effects of tiaprofenic acid are cystitis and bladder irritation. In the past eight years, the Adverse Drug Reactions Advisory Committee received 146 reports of cystitis or dysuria where tiaprofenic acid was the sole suspected agent.

Result: Once Surgam® was stopped, her symptoms resolved withiu a couple of weeks.

How was her osteoarthritis managed?

The patient was still in pain with her arthritis. Different treatments were tried, paracetamol to begin with. When that was not successful a different NSAID was prescribed that did not present the same side effects.

"I don't normally prescribe Surgam® and was unaware of its extra potential to cause cystitis, causing a four month delay in making a correct diagnosis."

– GP reporting this experience

Lessons Learned

- Just because a medication has been long-standing, it doesn't mean it cannot cause new symptoms. This woman had been on Surgam® without trouble for ten years before her cystitis developed.
- If someone else prescribes a drug that you're not familiar with, read up about it.

If you wish to share your experience with other GPs in future issues of NPS News, send details to the Editor, NPS News, 9 Leichhardt Street, Darlinghurst 2010, Email: sjackson@zip.com.au. Future topics are antibiotics, benzodiazepines, and treatment for chronic obstructive pulmonary disease and hypertension.

Managing gastrointestinal risk:

Is misoprostol (Cytotec®) helpful?

Misoprostol has been shown to reduce the incidence of serious gastrointestinal complications by 0.4% compared to placebo.[1]

An economic analysis of the study however did not justify the cost in the majority of cases (>$250,000 per complication prevented).[2]

It is more cost-effective in the small subgroup of high risk patients with a history of peptic ulcer or gastrointestinal bleeding and/or elderly patients with concomitant heart disease.

A recent trial shows misoprostol given twice or three times daily offers substantial protection against endoscopically visualised NSAID ulcers and is better tolerated than four times a day.[3]

Misoprostol should not be used in women of childbearing age.

NSAIDs – *products available*

If a trial of paracetamol has been unsuccessful and an NSAID is required use low doses of the lower risk agents (ibuprofen and diclofenac) for the shortest possible time. Addition of an intermittent NSAID to regular paracetamol may produce additive benefit and limit the dose of NSAID required.

diclofenac (Diclohexal®, Fenac®,Voltaren®, Voltaren Rapid®)

diflunisal (Dolobid®)

ibuprofen (ACT-3®, Actiprofen®, Brufen®, Nurofen®, Rafen®)

indomethacin (Arthrexin®, Hicin®, Indocid®, Indomed®)

ketoprofen (Orudis®, Orudis SR®, Oruvail SR®)

ketorolac (Toradol®)

mefenamic acid (Mefic®, Ponstan®)

naproxen/naproxen sodium (Anaprox®, Inza®, Naprogesic®, Naprosyn®, Naprosyn SR®, Proxen SR®)

phenylbutazone (Butazolidin®)

piroxicam (Candyl®, Candyl-D®, Feldene®, Feldene-D®, Mobilis®, Mobilis D®, Pirohexal-D®, Pirox®, Rosig®, Rosig-D®)

sulindac (Aclin®, Clinoril®, Saldac®)

tenoxicam (Tilcotil®)

tiaprofenic acid (Surgam®, Tiafen®)

Toxicology: paracetamol

In this topic:

For pharmacological information, see Paracetamol in 'Getting to know your drugs'.

Indicators of toxicity

Dose ingested

Poisoning with paracetamol can occur in the setting of either acute overdose or repeated supratherapeutic dose.

Acute overdose: Potential toxicity in adults with a single ingestion of more than 10 g and children with a single ingestion of more than 200 mg/kg.
Repeated supratherapeutic overdose: Risk of paracetamol hepatotoxicity is associated with:
more than 10 g (child: more than 200 mg/kg) in a single 24 hour period
more than 6 g (child: more than 150 mg/kg) per 24 hours during a 48 hour period
more than 4 g/day (child: more than 100 mg/kg/day) in patients with predisposing risk factors (chronic alcohol abuse, patients with potential glutathione depletion, such as in malnutrition, acute illness, or anorexia, or patients taking CYP450-inducing drugs).

Drug concentration

Acute overdose: Liver injury can occur in patients with paracetamol concentrations above the curved nomogram line (see Figure 14.22) and acetylcysteine [Note 1] should be given. A single nomogram line is now recommended. This has already been lowered by 25% to take into account any inaccuracy in the timing of ingestion and for safety in patients with potential risk factors.

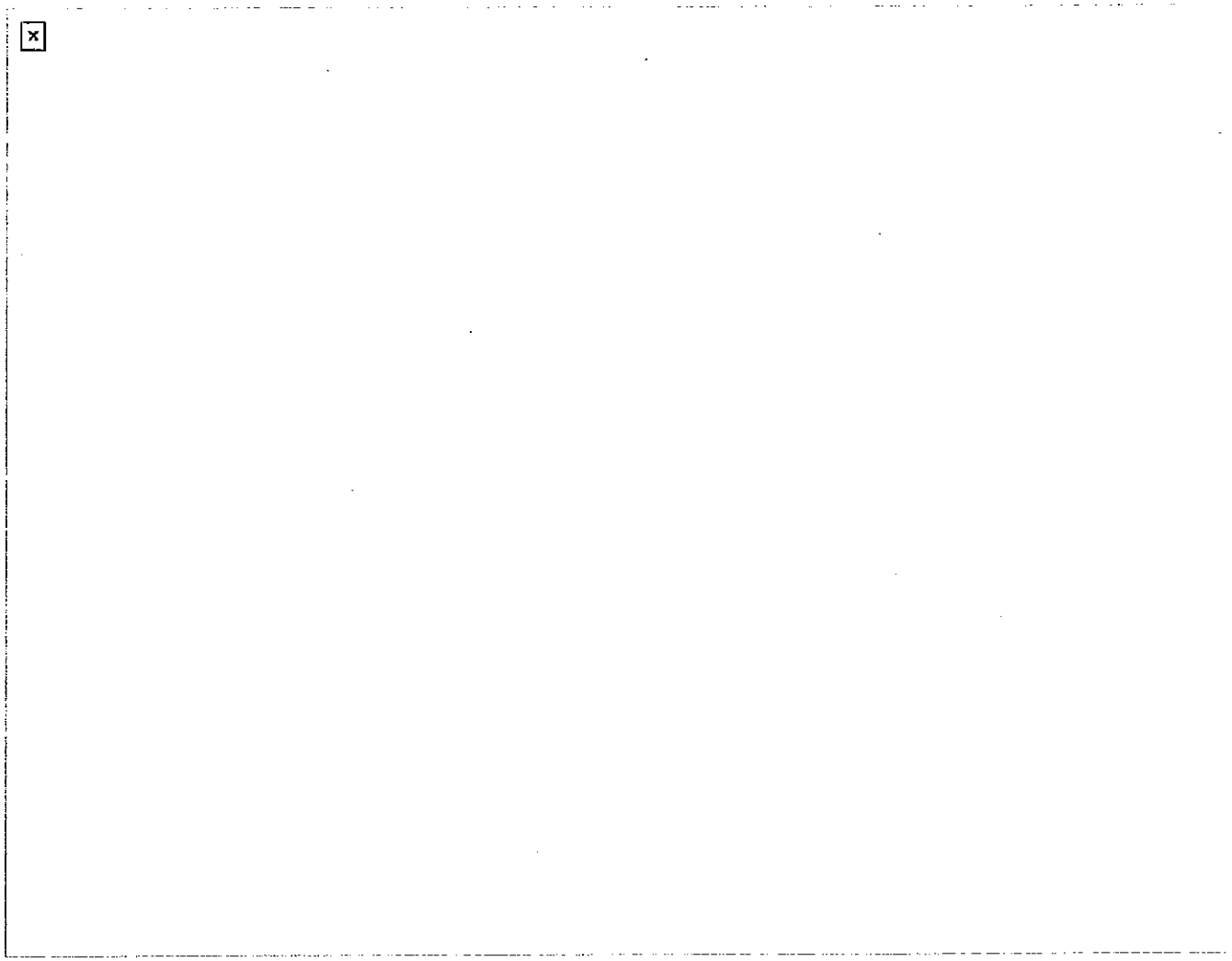
Delay to treatment

Delay to treatment with acetylcysteine is associated with worse outcome. If acetylcysteine is administered within eight hours of acute overdose, it is an effective antidote and prevents mortality.

Slow-release formulations of paracetamol

There is little evidence as to whether the risk of toxicity differs with slow-release formulations. The risk based on dose is identical, however the nomogram is not validated for these formulations. Until there is further evidence, the same nomogram should be used for slow-release formulations.

Paracetamol treatment nomogram (Figure 14.22)



Clinical presentation

Although paracetamol overdose is common it rarely results in severe liver injury or death.

Systemic effects include:

gastrointestinal effects: nausea, persistent vomiting, right upper quadrant abdominal pain
liver failure: hypoglycaemia, metabolic acidosis, severe coagulopathy and hepatic encephalopathy
renal impairment: may occur with severe liver failure or occasionally as isolated renal impairment
mild coagulopathy: a mild elevation in INR (no greater than 2.0) may occur early in the absence of liver failure.

Most patients present with acute poisoning (single overdose ingested) where the clinical sequelae are fairly predictable based on the dose ingested. However, repeated supratherapeutic ingestion can occur, for example in the following common clinical situations:

ingestions of more than 150 to 200 mg/kg daily for a period of a few days, usually for severe pain such as dental pain
repeated ingestion of combination products of paracetamol and codeine for weeks to months usually to obtain the codeine
use of supratherapeutic doses in unwell and dehydrated children for greater than 48 hours.

The risk assessment in patients with repeated ingestion of supratherapeutic doses is difficult and the paracetamol treatment nomogram should not be used. All patients with abnormal liver function tests should be treated with acetylcysteine. Otherwise the Dose ingested is the only predictor of toxicity and the use of acetylcysteine should be based on this. It is usually safer to err on the side of caution and commence acetylcysteine in many cases although this can be discussed with a clinical toxicologist.

Key investigations

paracetamol concentration: all patients with deliberate self-poisoning.
liver function tests (including AST, ALT, INR)
blood glucose level
electrolytes and renal function.

Treatment

Circulation

Ensure rehydration and maintenance intravenous fluids, see Table 14.4.

Decontamination

Charcoal should be used in cooperative patients who have ingested more than 200 mg/kg (children) or 10 g (adults) of a solid dose form of paracetamol within one hour of the time of presentation. Decontamination should not be used if liquid preparations have been ingested as liquid preparations are absorbed far more rapidly than solid dose forms. Decontamination is not generally indicated in children because they have usually taken a liquid preparation. In rare instances when a child may have ingested a solid dose form of paracetamol, the small benefit of charcoal does not outweigh the risks and difficulty in administering charcoal to a child unless they will drink it themselves.

Use:

activated charcoal 50 g (child: 1 g/kg to a maximum of 50 g) orally or via orogastric or nasogastric tube, within 1 hour of the estimated time of ingestion. Patients must be able to protect their airway or be intubated.	Pregnancy Breastfeeding

Liver failure

Any patient who develops signs of liver failure, including hepatic encephalopathy, hypoglycaemia, severe coagulopathy, metabolic acidosis or acute renal failure should be referred to a specialist liver unit.

Specific pharmacological therapies

Antidotal therapy: acetylcysteine

Timely use of acetylcysteine can prevent hepatotoxicity after paracetamol overdose.

Indications

If the patient presents within 8 hours of ingestion: acetylcysteine should be commenced if the drug

concentration is above the curved nomogram line, see Figure 14.22. In patients presenting within 4 hours of ingesting a paracetamol overdose, acetylcysteine can be withheld until a 4-hour concentration is measured, if this result will be available within 8 hours.

If the patient presents 8 or more hours after ingestion (or where the paracetamol concentration will not be known for 8 or more hours postingestion): acetylcysteine should be started, then ceased if the paracetamol concentration indicates that treatment is not required and if liver function tests (LFTs) are normal.

If the patient presents an unknown time after ingestion of a toxic dose (more than 200 mg/kg) or presents with abnormal LFTs following a paracetamol overdose: acetylcysteine should be administered.

If patients have ingested repeated supratherapeutic doses of paracetamol at potentially toxic levels (see Dose ingested), or who have abnormal LFTs: acetylcysteine should be administered.

Dose

Use:

acetylcysteine 150 mg/kg IV infusion, over 15 to 60 minutes
then acetylcysteine 50 mg/kg IV infusion, over 4 hours
then acetylcysteine 100 mg/kg IV infusion, over 16 hours.

Pregnancy
Breastfeeding

In patients who develop abnormal liver function tests, liver failure or where treatment is started after 8 hours from ingestion, an extended duration of therapy is appropriate. Most experts would continue acetylcysteine until after the peak in the AST, ALT and INR but advice can be obtained from a clinical toxicologist.

Non– IgE-mediated anaphylactic reactions may occur with acetylcysteine in 10 to 25% of cases with rash, urticaria, flushing, bronchospasm and rarely, hypotension. If such reactions occur, cease the infusion and recommence at a slower rate. Anaphylaxis should be treated according to a standard protocol, see Anaphylaxis. Such reactions may be more common in asthmatics. Reactions are highly unlikely to occur more than an hour after completion of the initial loading dose.

Monitoring and disposition

Criteria for discharge: Asymptomatic patients with a paracetamol concentration under the nomogram line require no further medical treatment.

Patients treated with acetylcysteine within 8 hours of ingestion may be discharged once the 20-hour regimen is complete.

Patients who develop severe liver failure should be offered consultation with a specialist liver unit.

Note 1: Acetylcysteine (rINN) is also commonly known as N-acetylcysteine and therefore the abbreviation to NAC will be found in many texts and local protocols.

Key references for this topic

Topic

Key references for this chapter

Other resources:

Clinical Evidence (subscription required)
Cochrane reviews

Paracetamol overdose

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors

If the patient
a, Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
Or
b, Regularly consumes ethanol in excess of recommended amounts.
Or
c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

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[redacted]

19 January 2011

Comments by [redacted] to the Advisory Committee for Medicines Scheduling – Meeting of 23 February 2011

Proposal

Ibuprofen – proposal to amend part (a) of the current Schedule 2 ibuprofen entry to increase the Schedule 2 limit on liquid preparations to at least 8 g or less (currently is 4 g or less).

[redacted] position

[redacted] supports the proposal to amend the Schedule 2 ibuprofen entry in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for manufacturer packs of liquid preparations to contain up to a maximum of 8 grams or less. This would facilitate the availability of larger pack sizes of stronger products for use in older age groups, and would mean that the non-prescription availability of ibuprofen would be on an equivalent footing to that for paracetamol.

Contact person:

[redacted]

[redacted]

Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) which is primarily used for the relief of nociceptive pain associated with tissue damage or inflammation. NSAIDs exert their main effect by inhibition of cyclo-oxygenase (COX), with consequent reduction in the synthesis of pro-inflammatory prostaglandins from arachidonic acid. This occurs at both peripheral sites in the body and the CNS.

Ibuprofen also has antipyretic effects and is used to alleviate discomfort associated with feverous conditions.

Ibuprofen is a non-selective COX inhibitor with a recommended paediatric oral dose of 8 to 10 mg per kilogram at eight hourly intervals, up to a maximum daily dose of 200 mg[1]. It is the most widely used NSAID in Australian children and has been available without a prescription since 1998[2].

Comments

Without having background information on the request to consider increasing the Schedule 2 limit on liquid preparations of ibuprofen, we have assumed that it is to facilitate access to stronger preparations for older children in quantities equivalent to that available for liquid paracetamol products. With this in mind, [redacted] has considered the proposed amendment to the Schedule 2 ibuprofen entry, and provides the following comments with consideration given to the scheduling criteria provided in the *Scheduling Policy Framework for Medicines and Chemicals*[3].

1. Paracetamol and ibuprofen are the main non-prescription analgesics used for treating pain and fever in children. Both are available as Schedule 2 products in a range of strengths for paediatric use from infancy to 12 years. In general, these medicines are safe and effective when used at their recommended doses[2], and although paracetamol is generally regarded as the preferred first choice, there are situations where one may be more appropriate than the other.

   [redacted] supports the Schedule 2 listing of paediatric analgesics containing paracetamol or ibuprofen as it provides parents with reliable access to these medicines through the 5000 plus community pharmacies throughout Australia, many of which have extended trading hours to facilitate after-hours access. The quality use of these medicines can be attained with appropriate labelling and packaging supported by assistance from trained pharmacy assistants with the capacity for pharmacist intervention if required.

   With paediatric medicine, doses vary significantly according to the age and weight of the child, and children are equally at risk of adverse events. With the availability of a variety of products with the same brand naming for different age groups, and possibly even different indications (e.g. cold and flu versus analgesic), it is essential the parents or carers of children have access to professional support to ensure they have the right dose for the right medicine for the right condition.

   Having these products available in Schedule 2, pharmacy assistants can assist parents or carers with the selection of appropriate analgesic/antipyretic products when

[redacted]

needed. Pharmacy assistants are trained to refer to the pharmacist for situations beyond their scope of practice, such as checking dosing schedules.

2. Nurofen® for Children, as one of the most well-known ibuprofen brands available for paediatric use, is registered on the Australian Register of Therapeutic Goods (ARTG) as:
    - Baby 3+ months; strength of 40 mg/ml (ARTG 108772)
    - 1-5 years; strength 100 mg/5 ml (ARTG 118807)
    - 5-12 years; strength 100 mg/5 ml (ARTG 150239)

    It is interesting to note that the product registered for the 5-12 year age group is the same strength as that for the 1-5 year age group. Compare this to Schedule 2 paracetamol products which has different strengths available for different age groups:
    - Children's Panadol® 1-5 years; strength of 24 mg/ml (ARTG 178300)
    - Children's Panadol® 5-12 years; strength of 48 mg/ml (ARTG 178302)

    Having stronger products available for older age groups is sensible in that smaller volumes of medicine are given at any one time to a sick child, so adherence is improved, and generally, these products are more cost-effective for consumers to purchase.

    Under the current Schedule 2 ibuprofen entry, the 4 gram limit for liquid products means that 200 ml is the maximum pack size for a product with a strength of 100 mg/5 ml. Should a product of 200 mg/5 ml be available, it would be limited to a maximum pack size of 100 ml.

    [redacted] supports increasing the pack limit to 8 grams of ibuprofen, which would allow the availability of larger quantities of a stronger product for the older age group. Along with appropriate labelling and packaging, pharmacists would also be readily available to advise parents or carers of the correct dosage schedule for their children.

Conclusion

[redacted] supports the proposal to amend the Schedule 2 ibuprofen entry in the SUSMP for manufacturer packs of liquid preparations to contain up to a maximum of 8 grams or less. This would facilitate the availability of larger pack sizes of stronger products for use in older age groups, and would mean that the non-prescription availability of ibuprofen would be on an equivalent footing to that for paracetamol.

Reference Sources:

[1] eTG November 2010; Therapeutic Guidelines : Analgesic 2007; http://online.tg.org.au/complete/
[2] Sean Beggs; Paediatric analgesia; Australian Prescriber 2008; 31:63-5
[3] National Coordinating Committee on Therapeutic Goods Scheduling Policy Framework for Medicines and Chemicals – 1 July 2010; www.tga.gov.au

[redacted]

[redacted] a fixed dose combination of Ibuprofen and Paracetamol

1) **Provides superior efficacy over its active components in relief of acute pain from molar extractions**
   Offers a safer and usually more efficacious alternative to single agent analgesic drugs including opioids and opioid (including codeine) combination analgesics.

[Please note confidential sections are highlighted in yellow and should be redacted from any publically released documents.]

[redacted]

In the past few years there has been increasing attention on the safety of commonly prescribed or OTC available analgesic drugs. For NSAIDs regulators have focussed on the gastrointestinal bleeding risks with higher and longer NSAID doses, and the more recently recognised risks of thromboembolic events even with non Cox selective NSAIDs. With paracetamol and diclofenac there has long been, and more recently a more intense examination of the risks of hepatic injury, most especially with higher than approved doses. Opioid drugs, including codeine, have gathered huge attention because of their side effects, the risks of addiction and of fatalities with accidental overdosage.

These widespread safety concerns are addressed by the formulation and dosing of [redacted] which combines paracetamol with ibuprofen at their approved daily OTC doses, and has shown superior efficacy over its active ingredients, and in recent published studies similar fixed dose combinations have shown superior efficacy over codeine containing fixed dose combination drugs. A very recent extended epidemiological study of the safety of co-prescribed ibuprofen with paracetamol has described this usage as safe as the individual drugs given alone. [redacted] then provides a safe and effective alternative to paracetamol or ibuprofen when more analgesia is required, is probably superior in efficacy to analgesic combinations with codeine, and avoids the risk of using opioids of any form.

[redacted]*should become the first choice when greater pain relief is needed if single agent paracetamol or an NSAID are insufficient and before moving to any opioid either singly or in combination.*

[redacted]

[redacted] is a film coated tablet containing ibuprofen 150 mg with paracetamol 500 mg for relief of acute pain, taken as one to two tablets up to 4 times a day so the maximum accumulated 24 hour doses accumulate for ibuprofen 1200mg and paracetamol 4000 mg, the currently approved maximal OTC doses internationally for both active ingredients.

[redacted] is also carefully designed to minimise patient confusion in that it is labelled to provide the same dosing frequency as paracetamol which is already a well known drug. There is another combination in regulated markets (Paracetamol 500mg + Ibuprofen 200mg) given three time a day. In the event that this combination is confused with standard paracetamol dosing the daily ibuprofen dose would exceed that of the normal OTC daily dose for ibuprofen i.e. if 2 tablets were taken 4 times a day then the total daily ibuprofen dose would be 1600mg/day rather than 1200mg/day. In this respect the two combinations differ and this risk is minimised with [redacted]

[redacted]

a) The Toxicity and Safety of the drug

[redacted] comprises two well characterised drugs: paracetamol and ibuprofen. Their clinical safety has been well defined over decades. [redacted] The clinical safety of both drugs is well described in multiple publications and regulatory reviews. The prime risks for paracetamol are liver injury almost always in overdose situations but with higher risks in patients with alcohol abuse and malnutrition.

Ibuprofen as a representative of the non-Cox selective NSAID class carries the class risks of triggering gastro intestinal bleeding and thromboembolic events. Ibuprofen was selected as the NSAID for this fixed dose combination as it has extended safety record as an OTC drug over decades, its record at OTC doses suggest it has the lowest or close to lowest risk of inducing gastrointestinal bleeding *(Henry et al. 1996; Henry et al. 2003)* and recent EMEA epidemiological evaluation of the risks of thromboembolic events suggested that the OTC approved daily dose of Ibuprofen showed no higher risks than placebo *(EMEA/CHMP/410051/2006 2006)*.

The Maxigesic pivotal phase 3 clinical study in patients undergoing molar extraction showed, over a 48 hour period, a statistically superior efficacy for the combination over either paracetamol or ibuprofen, each administered at their approved OTC maximum daily doses *(Merry et al. 2010)*.

[redacted]

The two drugs do not share metabolic pathways so their co-administration should not lead to any adverse additive or synergistic effects based on their metabolism. [redacted] From the clinical studies, the published literature and a recent extensive epidemiological review there appear to be no adverse consequences of using the two agents together. *De Vries et al* (2010) in a review from the UK General Practice Research Data Base within the MHRA evaluated a study population of 1.2 million patients who were prescribed paracetamol alone, or ibuprofen alone or the two drugs concomitantly *(De Vries et al. 2010)* . There did not appear to be any modification of the known risks of either active drug when the two were co-administered.

This is consistent with more recent information on the mode of action of paracetamol where it is identified that it acts centrally rather than through COX inhibition. A recent review *(Bertolini et al. 2006)* summarises the mode of action:

"In spite of the remarkable feature that clearly distinguishes paracetamol from non-steroidal antiiflammatory drugs (NSAIDs) – that is, the absence of antiinflamatory activity (with very few exceptions) – the aim to demonstrate that the mechanism of action of paracetamol and NSAIDs is the same has been steadily and perversely pursued."

The conclusion was that paracetamol acts as a pro-drug, with the active metabolite (AM404) being formed in the brain through conjugation of the deactylated derivative of paracetamol (p-aminophenol) with arachidonic acid, by the action of fatty acid amide hydrolase (FAAH). At analgesic doses of paracetamol, AM404 that is formed in brain regions indirectly activates cannabinoid, CB_1 receptors and directly activates TRPV1 receptors.

Martindale Extra Pharmacopioea also states that *"Paracetamol, a para-aminophenol derivative, has analgesic and antipyretic properties. It does not possess any anti-inflammatory activity"*. This is again consistent with lack of COX inhibition.

b) **The Risks and Benefits of [redacted].**

How does [redacted] compare with other analgesic drugs? How might it be positioned?

The risks of this fixed dose combination is that of each of its active ingredients and, as described above, a major epidemiology study *(De Vries et al. 2010)* showed that the co-administration of ibuprofen with paracetamol is not accompanied by any apparent increase in adverse outcomes.

The range of alternate analgesic drugs include single agent paracetamol and NSAIDs including ibuprofen and diclofenac, paracetamol in combination with caffeine, all opioid combination drugs and opioids themselves as single agents. [redacted] offers benefits in a number of directions.

i) Paracetamol

Paracetamol has been the front line analgesic drug for decades in most countries of the world. Its OTC dose and its prescription maximum daily dose is 4000 mg. While it is relatively free from side effects there are well recognised risks of hepatic injury with higher doses. This has been the subject of a major TGA review in 2003 and led to a restriction in pack sizes and also in the UK. More recently an FDA Advisory Committee has reviewed this risk and made a number of recommendations. Factors contributing to the risks are higher than approved daily doses, confusion from labelling issues where additional analgesia is needed but a second analgesic preparation might also include paracetamol, usually in combination, leading to an overdose situation. This situation has led to some restrictions in the availability of pack sizes to limit the risks. [redacted] includes paracetamol and at 2 tablets 4 times daily does reach the maximum approved daily dose of paracetamol. But the [redacted] advantage rests with its superior efficacy over the same dose of paracetamol alone reducing the risks of a patient taking more of their first in hand pain relief.

Thus in patients taking maximum doses of paracetamol but who need more pain relief their choices are:

- Increase the dose of the drug. This is not possible as they then enter the dose range of increased risk of liver injury
- Substitute an NSAID, which may or may not provide greater pain relief. But which one, and will it provide greater efficacy than the paracetamol?
- Add an NSAID and here [redacted] has done that already and backed that choice with robust clinical data.
- Move to a codeine or more potent opioid containing drug or a single dose higher potency opioid with all the attendant risks and side effects. [redacted] offers a clear alternative: greater efficacy than maximum doses of paracetamol while avoiding opioid or opioids combinations. There is also data that suggests the combination of ibuprofen with paracetamol offers superior efficacy to either paracetamol or ibuprofen combined with codeine at 30mg or 25.6 mg respectively *(Daniels et al. 2010)*. 30mg doses or more of codeine in analgesic drugs alone or in combination are now schedule 4 and so require a prescription.
- A very recent review by *Murnion* (2010) concluded that the addition of codeine to paracetamol has questionable additional efficacy at the doses most commonly used in Australia that is less than 30mg *(Murnion 2010)*.
- The dose of [redacted] is 1 to 2 tablets up, to 4 times a day so offering maximum flexibility with superior efficacy over its active components at maximum daily doses.
- Move to a fixed dose combination of paracetamol with caffeine which has been heavily promoted recently. The data are over 18 years old, suggest the added efficacy from the addition of caffeine is around 10% and fails to record the anticipated side effects of disturbance of sleep and tachycardia that would be expected by such a combination. In

contrast [redacted] adds over 30% in efficacy and for minimal penalty in side effects and risks.

ii) NSAIDs

All NSAIDs appear to carry a risk of triggering a gastrointestinal bleed, especially with higher doses, taken for longer and in older patients. Ibuprofen was selected as the best characterised NSAID for both OTC use and at higher doses by prescription. It has reportedly one of the lowest risks of gastrointestinal bleeding, especially at OTC doses which are those used for Maxigesic *(Henry et al. 1996)*. The recent EMEA opinion of the risks of thromboembolic events for non-Cox 2 selective agents concluded that, at the approved OTC daily doses of 1200mg, ibuprofen appeared to show risks no greater than placebo *(EMEA/CHMP/410051/2006 2006)*. In December 2009 FDA issued a warning about the possible hepatic injury risks of diclofenac which would have ruled out this NSAID as a possible combination with paracetamol *(FDA Safety Alerts December 4 2009)*.

So where patients are taking an NSAID such as ibuprofen for pain relief, but need more intense analgesia they have some choices:

- Increase the dose of the NSAID, but this requires a prescription and enters the higher risks range for gastrointestinal bleeding and thromboembolic events.
- Move to an opioid or opioid including codeine combination with their inherent risks (See section below).
- Add paracetamol which is a common clinical decision from the IMS co-prescription data showing in 2007 over 1.4 million co-prescriptions for these two drugs in the UK and almost 3.9 million in the USA.
- The simpler choice is to use [redacted] where the doses have been combined from the well characterised and approved OTC doses and where there is robust clinical data of the analgesic superiority of the combination over each of its active drugs taken alone.

[redacted]

iii) Opioid Drugs alone or in Combination

Recently in Australia and in the USA there has been extensive publicity about the risks of opioid drugs for both their addictive qualities and their association with fatal drug overdosage. Compared with paracetamol, ibuprofen and the two in combination as [redacted] the opioids present the following hazards and risks.

- The carry significant side effects such as constipation, dizziness, nausea, fatigue, somnolence. These side effects are more pronounced in the elderly.

- They are addictive and now present a major public health problem internationally. In 2009 the Royal Australasian College of Physicians, the Royal Australian College of General Practitioners, the Faculty of Pain Medicine of the Royal Australian and New Zealand College of Anaesthetists and the Royal Australian and New Zealand College of Psychiatrists published a combined *Prescription Opioid Policy* to prevent the problems associated with opioid use. They quoted the worrying figures that up to 20% of the Australian population suffer chronic non-malignant pain in need of medication.
- Prescription opioids are increasingly associated with fatal overdose. A position paper on this topic in November 2010 New England Journal of Medicine titled "*A Flood of Opioids, A Rising Tide of Deaths*" emotionally and dramatically highlighted this problem. It concluded from CDC data that accidental fatal drug overdosage from opioids in the USA caused almost 11,500 deaths in 2007.
- Codeine is not innocent but is a member of the opioid drug class and has been the subject of some supply restrictions already in Australia. But there is gathering evidence that the grandfathered view that analgesics combined with codeine provide significantly superior pain relief might well be mistaken *(Murnion 2010)*. More recent data on the value of ibuprofen and paracetamol fixed dose combinations has come from some recent publications on a range of single dose studies using a combination of 500 mg paracetamol with 200mg ibuprofen used at either one or two doses. The more interesting comparison came with the demonstration that 1000mg paracetamol with 400mg ibuprofen showed superior efficacy to paracetamol 1000mg plus codeine 30mg and to ibuprofen 400mg plus codeine 25.6mg *(Daniels et al. 2010)*. As [redacted] at two tablets delivers a dose of paracetamol 1000mg and ibuprofen 300mg how might the lower dose of the published study perform? The investigators showed that 500mg paracetamol plus 200mg ibuprofen showed superior efficacy to paracetamol 1000mg plus codeine 30mg and comparable to ibuprofen 400mg plus codeine 25.6mg. This strongly suggests that [redacted] at two tablets taken as a single dose will show superior efficacy to either paracetamol 1000 mg plus codeine 30mg and to ibuprofen 400mg plus codeine 25.6mg.
- So where there is need for additional analgesia, caution has to be given before deciding that an opioid or an opioid combination is the next choice, for the side effects and the risks seem barely to be balanced by the data and the first choice should be [redacted] In effect [redacted] should be considered the first step after single dose paracetamol or an NSAID and always before moving to an opioid or opioid containing combination.
- Currently the indications for [redacted] are for acute pain, [redacted]

[redacted]

c) The potential hazards of [redacted]

The constituents of the fixed drug combination are well known. There have been no unexpected adverse effects from either clinical studies nor from extended epidemiological surveys.

The potential hazards are those already associated with the single component drugs by themselves. These warnings can be clearly dealt with on the packaging.

It is important that the warnings also detail not using with other medicines containing either paracetamol or ibuprofen. Furthermore the labelling should clearly indicate the active ingredients.

Smaller pack sizes such as 30s for a few days use would seem to be appropriate for an S2 scheduling. We do not believe that it is appropriate to down-schedule this combination so that a smaller pack size could be available in a grocery outlet. An S2 scheduling allows for a patient to seek Pharmacy staff advice where required.

d) The extent and patterns of use of [redacted]

The drug is indicated for the relief of acute pain at 2 tablets up to 4 times a day. For acute use in smaller pack sizes, the combination would be used in cases where a single agent such paracetamol alone or ibuprofen alone does not provide sufficient analgesia.

The use of [redacted] would be expected to displace existing use of opioid combination analgesics with their inherent serious public health concerns, as opposed to replacing existing use of either paracetamol or ibuprofen alone except when patients require additional pain relief.

e) The dosage and formulation of [redacted]

The proposed label for relief of acute pain is 1 to 2 tablets up to 4 times a day. This provides at maximum daily doses paracetamol 4000 mg and ibuprofen 1200 mg, both their maximum approved daily doses. As patients generally self medicate with pain relief this flexibility adds to the safer use of the drug and especially as it delivers superior efficacy than either paracetamol or ibuprofen alone.

[redacted] is carefully designed to be a stronger version of paracetamol. Paracetamol dosing is well known and this would avoid confusion in dosing intervals and daily doses.

It is presented as a scored film coated tablet suitable for use in adults and children over 12 years of age.

f) The need for [redacted] taking into account its toxicity compared with other substances available for a similar purpose

The benefits of [redacted] in today's analgesic drug environment have been outlined in section b) above under the risks and benefits of the drug. Like other analgesic drugs it would be considered as schedule 2 as it avoids the use of codeine or other opioids.

[redacted] with its fixed dose combination of ibuprofen with paracetamol, each at the OTC approved daily doses when a patient takes 2 tablets 4 times a day, provides a new choice for patients and for pharmacists where additional pain relief is needed beyond single agent paracetamol or and NSAID alone. It is the logical alternative to all codeine containing combinations superior in efficacy and safety.

Although there also exists a combination analgesic paracetamol and caffeine, this provides little additional analgesia with additional analgesia of 10% at best *(Laska 1983)*. Furthermore the labelling warning to avoid additional caffeine intake is difficult in terms of patient compliance. The data for this combination are minimal and have minimal safety or side effect data as the addition of caffeine is likely to add materially to disturbances of sleep and tachycardia. In contrast [redacted] provides a greater than 30% additional analgesia with minimal addition of side effects or risks.

With the current focus on the safety of analgesic drugs the place of [redacted] becomes clearly defined. The ibuprofen and paracetamol doses have been selected as the currently internationally approved OTC daily maximum doses. The risks of using the drug combinations are no different from those of its two active ingredients and at their approved OTC doses. The benefits rest with its superior efficacy over its active ingredients, a benefit purchased without adding to the safety burden. There is no risk of substance abuse beyond the risks associated with paracetamol and ibuprofen. Overall [redacted] represents a gain from the public health perspective as a potent analgesic which avoids the risks of opioids, or opioid combinations where analgesia from paracetamol and NSAIDs is insufficient.

- [redacted] shows analgesic superiority over maximum daily doses of its active constituents, ibuprofen and paracetamol
- Ibuprofen and paracetamol engage quite distinct metabolic pathways, different modes of action and in extensive epidemiological studies have not revealed any additive or unexpected safety concerns.

- Ibuprofen has decades of safety data and at the OTC maximum daily dose carried minimal risks of gastrointestinal bleeding and thromboembolic events.
- [redacted] offers a first line alternative to single agent analgesia of paracetamol or any NSAID in cases where additional analgesia is required, without breaching the maximum OTC doses of the single agents yet providing significant additional efficacy
- [redacted] offers a logical and robust first choices alternatives for codeine-containing combination drugs both as it avoids any opioid side effects or addiction risks and as emerging data suggests it is likely to be significantly more efficacious.
- [redacted] offers a first line alternative to single dose opioids or other opioid combinations as it offers robust efficacy and avoids the side effects and risks of opioids.
- Scheduling [redacted] as S2 at pack sizes of 30 tablets and as Pharmacist where larger numbers are required appears sensible and logical.

g) The potential for abuse

There has been no evidence that either paracetamol or ibuprofen are addictive.

h) The purposes for which [redacted] is to be used

The proposed label for the drug is for short term use for relief of acute pain.

i) Any other matters for the Committee relating to public health

The current analgesic drug environment is facing a significant re-review of the safety of all classes. From the public health perspective the issues accompanying use of drugs containing opioids, including codeine, have required various restrictions on availability to be implemented. In so doing the public faces some limitations in access to more potent analgesic drugs. [redacted] fills that gap while avoiding the various adverse effects and risks of opioids.

Reference:

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Daniels, S. E., Aspley, S., Reader, S., Mehlisch, D. R. and Southerden, K. A. (2010). A comparison of the analgesic efficacy and tolerability of a combination of ibuprofen 400 mg plus paracetamol 1000 mg, a combination of ibuprofen 200 mg plus paracetamol 500 mg, a combination of ibuprofen 400 mg plus codeine 25.6 mg, a combination of paracetamol 1000 mg plus codeine 30 mg, and placebo in postoperative dental pain following third molar extraction. Presented at 13th World Congress on Pain, Montreal Quebec, Canada August 29-Sep 02., Premier Research Group.

De Vries, F., Setakis, E. and Van Staa, T. P. (2010). "Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes." British Journal of Clinical Pharmacology **70**(3): 429-438.

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Murnion, B. P. (2010). "Combination analgesics in adults." Australian Prescriber **33**(4): 113-115.

2.1.4 Ibuprofen+paracetamol - submission 2/4

[redacted]

18 January 2011

The Secretary
Medicines & Poisons Scheduling,
Office of Chemical Safety and Environmental Health (MDP 88)
GPO Box 9848, Canberra ACT 2601
Email: smp@health.gov.au

Fax: 02-6289 2500

Re: Meeting of the Advisory Committee on Medicines Scheduling – 23 February 2011. Invitation for Public Comment

In this document, XXXXX would like to submit further comment in relation to the scheduling of ibuprofen 200 mg and paracetamol 500 mg combination which is to be discussed at the forthcoming meeting of the ACMS on 23 February 2011.

XXXXX has previously submitted comments for consideration at the June 2010 meeting. The outcome of the June 2010 NDPSC meeting was as follows:

Resolution 2010/59 – 43
The Committee agreed that the current scheduling of ibuprofen and paracetamol remained appropriate i.e. 200 mg or less of ibuprofen in combination with 500 mg or less of paracetamol, in packs of not more than 100 dosage units, remained Schedule 2.

Since the June 2010 NDPSC meeting, an identical product under the tradename of NUROMOL® has been registered in the UK by RB Healthcare (UK) Ltd. The UK Medicines and Healthcare products Regulatory Agency (MHRA) approved the product in September 2010 as a Pharmacy-Only Medicine[2]. This was also approved in Poland in December 2010.

Following the dissolution of NDPSC in July 2010, the following item is tabled again for consideration by the ACMS in its first meeting in February 2011:

Item 1.3 Paracetamol + ibuprofen combination - consideration for a higher schedule

XXXXX would now like to take this opportunity to submit comment to the new ACMS.

XXXXX

Since early 2010, all OTC combination analgesics containing codeine (CACC) have been removed from Schedule 2 (S2) to either S3 or S4 leaving consumers with a more limited choice for pain relief. One available option for consumers is to increase the dose of the analgesics they are taking. This may lead to increased adverse effects.

XXXXX developed the fixed dose combination product of ibuprofen 200 mg/paracetamol 500 mg as an effective alternative to other non-prescription products, e.g. fixed combination opioid products, for the treatment of mild to moderate pain and fever in self-diagnosed self-limiting conditions. The rationale for the development of this fixed combination is combined efficacy, through the different and complementary mechanisms of action. This results in an 'additive' effect, i.e. greater pain relief than either single active alone, with no deterioration of the safety profile[1], [2], [3].

The proposed posology for 'ibuprofen 200 mg/paracetamol 500 mg tablet' results in a maximum daily dose of 1.5 g of paracetamol and 0.6 g of ibuprofen. The existing non-prescription maximum daily doses are 4 g for paracetamol containing products and 1.2 g for ibuprofen containing products. The product and the proposed posology therefore reduce the risk of exposure to paracetamol and ibuprofen, i.e. paracetamol and ibuprofen sparing, thus minimising the risk of unintentional or accidental overdose with paracetamol.

XXXXX would like to summarise the following matters under Section 52E of the Therapeutic Goods Act 1989 for the Committee's consideration:

(a) the risks and benefits of the use of a substance;

Ibuprofen and paracetamol have both been widely available for many years. They are both used for the treatment of the same minor ailments or symptoms e.g. headache, dental pain, arthritic and joint pain, menstrual pain, migraine, muscular pain, including sprains and strains[4]; that can be easily recognised and managed by the consumer and that are unlikely to be confused with more serious conditions.

A key benefit for responsible consumers who are used to self-medicating, is that the new ibuprofen/paracetamol combination provides an alternate safe and more effective pain relief than either paracetamol or ibuprofen as the only active ingredient. XXXXX maintains that S2 scheduling is appropriate as this will ensure that a pharmacist is available to provide advice and education to consumers on responsible use of the product.

Both ibuprofen and paracetamol have well-documented safety profiles[3]. There is a low and well-characterised incidence of adverse effects for both substances and this is shared by the combination, at the proposed dose.

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[1] Ong CKS, Seymour RA, Lirk P & Merry AF. Combining Paracetamol (Acetaminophen) with Nonsteroidal Antiinflammatory Drugs: A Qualitative Systematic Review of Analgesic Efficacy for Acute Postoperative Pain. Anesth Analg 2010; 110: 1170-9

[2] Public Assessment Report. Nuromol 200 mg/500 mg tablets (Ibuprofen/Paracetamol) 15 Sep 2010 http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con099698.pdf

[3] http://www.australianprescriber.com/magazine/31/3/63/5

[4] http://www.asmi.com.au/consumer/Self-Care-Products.aspx accessed 10/1/11

In addition, at the proposed maximum daily dose there is a reduction in the daily amount of both ibuprofen and paracetamol taken with the combination product, as opposed to the maximum daily dose of the individual components, thus minimising the risk of unwanted side effects. The exposure to paracetamol and ibuprofen is much less compared to paracetamol or ibuprofen when used as a single oral active as mentioned above.

The pharmacokinetic properties of ibuprofen and paracetamol when given in combination (400 mg ibuprofen and 650 mg paracetamol) have been examined in a repeat dose study[5]. Whilst Tmax for paracetamol in the combination was faster there were no other statistically significant differences in kinetic parameters when paracetamol and ibuprofen were administered in combination compared with either active alone. These data suggests that there are no pharmacokinetic interactions between ibuprofen and paracetamol that would give rise to safety concerns.

In a published retrospective cohort study to evaluate a range of safety outcomes e.g. upper gastrointestinal events, myocardial infarction, stroke, renal failure (excluding chronic), congestive heart failure, intentional or accidental overdose, suicidal behaviour and mortality in a population of 1.2 million patients prescribed ibuprofen and paracetamol concomitantly and compared these with safety outcomes in patients prescribed ibuprofen or paracetamol alone[6]. Specifically, these outcomes were assessed with reference to the dosage and treatment duration. The results showed that although there was considerable heterogeneity in the patient and exposure characteristics between groups, the relative rates (RRs) and hazard rate patterns were statistically similar for most safety outcomes between patients prescribed ibuprofen and paracetamol concomitantly and those prescribed ibuprofen or paracetamol alone. This suggests that concomitant use of ibuprofen and paracetamol does not increase risk of the various safety outcomes examined over use of paracetamol or ibuprofen alone.

Hence, whilst the benefits of the combination of paracetamol and ibuprofen is combined efficacy, through the different and complementary mechanisms of action; the risks in regard to upper gastrointestinal events, myocardial infarction, stroke, renal failure (excluding chronic), congestive heart failure, intentional or accidental overdose, suicidal behaviour and mortality are not increased.

(b) the purposes for which a substance is to be used and the extent of use of a substance

As with single actives in OTC use, the combination of paracetamol and ibuprofen is not intended for treatment of a chronic condition. The proposed indication for ibuprofen 200 mg/paracetamol 500 mg tablet is for the short-term relief of pain and fever and the proposed dosing regimen is 1 tablet every 8 hours, for a maximum of 3 days.

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[5] Wright CE, Antal EZJ, Gillespie WR & Albert KS. Ibuprofen and acetaminophen kinetics when taken concurrently. Clin Pharmacol. Ther 1983, 34 (5): 707-710

[6] De Vries F, Setakis E & van Staa T-P. Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes. Br J Clin Pharmacol 2010, 70 (3): 429-438

(c) the toxicity of a substance

Both ibuprofen and paracetamol have well-documented safety profiles. There is a low and well-characterised incidence of adverse effects for both substances and this is shared by the combination, at the proposed dose. Consumers are used to self-medicating with paracetamol and ibuprofen-containing analgesics and the contra-indications and warning on pack are familiar to them. The packaging and labelling of the combination tablet utilise the same warnings and contra-indications and will therefore be familiar. In addition, at the proposed maximum daily dose there is a reduction in the daily amount of both ibuprofen and paracetamol taken with the combination product, as opposed to the maximum daily dose of the individual components.

The greatest potential for harm with the combination lies in the potential for unintentional overdose due to consumer confusion regarding the constituents of the combination. In this respect ibuprofen 200 mg/paracetamol 500 mg tablet is no different from any other combination of simple analgesics. To minimise the risk of this occurring XXXXX undertakes to provide clear communication on pack and in educational and promotional material to both pharmacists and pharmacy assistants.

(d) the dosage, formulation, labelling, packaging and presentation of a substance

The dosage is as described above. The formulation is a film coated tablet.

The labelling meets the TGO 69 (including RASML) with appropriate warnings and contra-indications for paracetamol and ibuprofen and will therefore be familiar to the responsible self-medicating consumers. A copy of the proposed label is attached.

(e) the potential for abuse of a substance

To date, there is no evidence that either paracetamol or ibuprofen is associated with dependency, abuse or illicit use as individual actives. As a combination, it is therefore expected that ibuprofen 200 mg/paracetamol 500 mg tablet will not produce dependency. The likelihood of abuse, misuse and illicit use is low. In fact, in this regard the combination offers significant benefits over current strong pain products containing codeine, which may produce dependence and are open to abuse.

In NZ, an ibuprofen 150 mg/paracetamol 500mg combination has been scheduled for General Sale in pack sizes of 8 and 16 tablets and as Pharmacy only for pack sizes of 50 and 100.

Since th e UK MHRA a nd the Polish Autho rity ha ve cla ssified ibuprofen and paracetamol c ombination as a Pharmacy-Only Medicine [2], X XXXX requests t he ACMS to consider maintaining the Schedule 2 listing of ibuprofen 200 mg or less in combination with paracetamol 500 mg in pack sizes of up to 48 tablets.

Yours sincerely
XXXXX

XXXXX

[redacted]

19 January 2011

2.1.4 Ibuprofen+paracetamol - submission 3/4

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Email: SMP@health.gov.au

Invitation for public comment – ACMS meeting 22 February 2011

1.3 Paracetamol + Ibuprofen combination
Consideration for a higher schedule (currently in schedule 2)

[redacted] appreciates the opportunity to provide comment in relation to this issue. We wish to address relevant matters under section 52E of the Therapeutic Goods Act 1989 as these apply to the substances mentioned above: (a) risks and benefits; (c) toxicity; (d) labelling; (e) potential for abuse.

Introduction

Individually, Ibuprofen and Paracetamol are both classified as Schedule 2 substances in the SUSMP, with scheduling exemptions for certain small pack sizes.

Relevantly, the current Ibuprofen Schedule 2 entry includes oral preparations when labelled with a recommended daily dose of 1200 mg or less, in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units. Smaller packs are unscheduled, where Ibuprofen is the only therapeutically active constituent, if the prescribed labelling requirements are met.

Relevantly, the current Paracetamol Schedule 2 entry excludes tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when packed in blister or strip packaging or in a container with a child-resistant closure in packs of not more than 25 dosage units with the prescribed labelling requirements. Such excluded products are unscheduled.

[redacted] notes that the current policy in relation to the scheduling of products containing more than one poison is set out in the SUSMP under *Principles of Scheduling* as follows:

> *If a preparation contains two or more poisons, the provisions relating to each of the Schedules in which those poisons are included apply.*
>
> *Where it is not possible to comply both with a provision relating to one of those Schedules and with a provision relating to another of those Schedules, the provision of the more restrictive Schedule applies, unless a contrary intention is indicated in the Schedules or relevant legislation.*

Based on the above, the combination of Ibuprofen and Paracetamol ought to be Schedule 2.

[redacted]

Overview

[redacted] supports maintaining the Schedule 2 listing of the combination consistent with current policy guidelines.

52E(1)(a) Risks and benefits

Ibuprofen and Paracetamol both have a long history of safe use in Australia and both ingredients have well documented safety profiles.

The low risks associated with these ingredients are such that they are unscheduled in certain circumstances.

It is [redacted] position that the low risks individually associated with Ibuprofen and Paracetamol will similarly be associated with a combination of the two. [redacted] position on this matter is supported by a recently published retrospective cohort study[1] . The study included 1.2 million patients who were prescribed ibuprofen alone, paracetamol alone or concomitant ibuprofen and paracetamol. The authors examined the safety of the combination in comparison with actives alone.

The safety outcomes evaluated were upper gastrointestinal events, myocardial infarction, stroke, renal failure (excluding chronic), congestive heart failure, intentional or accidental overdose, suicidal behaviour and mortality.

The authors concluded that:

> *"There was considerable heterogeneity in the patient and exposure characteristics between groups. The RRs [relative rates] and hazard rate patterns were statistically similar for most safety outcomes between patients prescribed ibuprofen and paracetamol concomitantly and those prescribed ibuprofen or paracetamol alone. This suggests that concomitant use of ibuprofen and paracetamol does not increase risk of the various safety outcomes examined over use of paracetamol or ibuprofen alone."*

In the absence of evidence demonstrating an increased risk associated with the combination, [redacted] therefore suggests that current policy in relation to scheduling of combination products be applied.

52E(1)(c) Toxicity

Ibuprofen and Paracetamol both have well documented safety profiles and, as discussed above, there is evidence to show that combining the two actives will not be associated with increased risk.

52E(1)(d) Labelling

[redacted] acknowledges that combination products may contribute to unintentional overdose (with consumers taking multiple products containing the same active). However, this is an issue that can adequately be dealt with through product labelling and would be best addressed by the regulator.

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[1] de Vries F, Setakis E, van Staa TP. Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes. *Br J Clin Pharmacol*. 2010 Sep;70(3):429-38.

52E(1)(e) Potential for abuse

[redacted] is unaware of any evidence that Ibuprofen or Paracetamol (either individually or in combination with each other) are associated with dependence, abuse or illicit use.

Summary

The current scheduling of Ibuprofen and Paracetamol remains appropriate.

There is evidence that concomitant use of Ibuprofen and Paracetamol does not increase risk.

There is no evidence to suggest that a departure from scheduling policy is warranted for this particular combination.

We look forward to hearing the outcomes of the Committee's deliberations on this issue.

Yours faithfully,

[redacted]

19 January 2011

Comments by [redacted] to the Advisory Committee for Medicines Scheduling – Meeting of 23 February 2011

Proposal

Paracetamol + ibuprofen – consideration for a higher schedule. Currently in Schedule 2.

[redacted] believes that any combination analgesic must be scheduled. [redacted] supports the inclusion of small pack sizes of a fixed dose ibuprofen/paracetamol combination product to be included in Schedule 2 and that larger pack sizes would be more appropriately included in Schedule 3.

Contact person:

[redacted]

Background

Paracetamol is indicated for mild to moderate pain, having analgesic and antipyretic actions in the central nervous system (CNS). It has minimal anti-inflammatory action although it has the potential to suppress low-grade inflammation as seen in osteoarthritis. The recommended adult dose for paracetamol is 0.5-1 g every four to six hours, up to a maximum of 4 g per day.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) which is primarily used for the relief of nociceptive pain associated with tissue damage or inflammation. NSAIDs exert their main effect by inhibition of cyclo-oxygenase (COX), with consequent reduction in the synthesis of pro-inflammatory prostaglandins from arachidonic acid. This occurs at both peripheral sites in the body and the CNS. Ibuprofen is a non-selective COX inhibitor with a recommended dose of 200-400 mg every six to eight hours, up to a maximum daily dose of 2400 mg.

Paracetamol and ibuprofen are commonly prescribed together in clinical practice, however compliance can be poor with asynchronous dosing.[1]

Comments

[redacted] has considered the proposal for the schedule listing for fixed dose ibuprofen/paracetamol combination products, and provides the following comments with consideration given to the scheduling factors provided in the *Scheduling Policy Framework for Medicines and Chemicals* [2](Scheduling Framework).

1. The use of paracetamol in combination with a NSAID has been demonstrated to provide additive pain-relief.[3,4] The availability of a combination product provides consumers and clinicians with an effective and cost-effective product that simplifies the dosage schedule for both active ingredients.
2. Although having relatively safe profiles, the relative risk of these medicines, particularly in combination, warrants consumers accessing advice and support from a pharmacist or other appropriate health professional. This is achieved by inclusion within an appropriate medicine schedule of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).
3. [redacted] believes that small packs of an ibuprofen/paracetamol combination product meet the scheduling factors for Schedule 2 as defined within the Scheduling Framework.
    - The quality use of the product can generally be achieved by labelling and packaging and information provided by a pharmacy assistant, while the pharmacist is available for referral if required.
    - The use of paracetamol and ibuprofen, either alone or in combination, is relatively safe when taken within their recommended dosage range for short-term pain relief.
    - Neither paracetamol nor ibuprofen have any significant abuse potential, and the availability of a combination analgesic in Schedule 2 may also assist in reducing the reliance many patients have had to date on combination analgesics containing codeine.

- The risk profiles of both paracetamol and ibuprofen are well defined and capable of being managed with appropriate labelling and packaging with access to pharmacy support.

  Under current scheduling arrangements, small packs containing either paracetamol or ibuprofen as a single active ingredient are exempt from scheduling and larger pack sizes included in Schedule 2 of the SUSMP.

  Although ibuprofen can cause upper gastrointestinal side-effects and should be avoided in people with aspirin-induced asthma, the greatest risk [redacted] sees with an ibuprofen/paracetamol combination product are:

  i. the potential for cardiovascular harm from the use of NSAIDS
  ii. the potential for adverse effects on renal function from the use of NSAIDs
  iii. the potential for adverse effects on liver function from inadvertent overdosage on paracetamol by taking different paracetamol containing products at the same time. This risk is enhanced in alcoholics and chronic excessive drinkers[5]. Of interest is the recent safety advisory[6] from the United States Food and Drug Administration (FDA) on paracetamol (acetaminophen) where the strength of paracetamol in combination prescription products is being limited to 325 mg per dosage unit to minimise risks of severe liver injury and allergic reactions associated with paracetamol.

  These risks can be ameliorated through appropriate warnings on the pack and limiting availability to facilitate access to health professional advice when required.

- Appropriate labelling and packaging of small packs of a combination product with access to pharmacist advice if needed should adequately manage any risk of delaying diagnosis or treatment of more serious conditions.

4. The availability of small packs of an ibuprofen/paracetamol combination product in Schedule 2 could also have a positive impact on pharmacy workflow by having alternative therapies available without the need to always consult a pharmacist.

   As with any Schedule 2 medicine, pharmacy assistants will need suitable training to ensure they can adequately triage patients and refer to the pharmacist when appropriate. [redacted] would be pleased to collaborate with sponsors of combination products to assist in developing and implementing appropriate training modules.

5. [redacted] believes that larger pack sizes of an ibuprofen/paracetamol combination product meet the scheduling criteria for Schedule 3 as defined within the Scheduling Framework.

   - Patients requiring ongoing treatment of painful or inflamed conditions benefit from the intervention of a health professional such as a pharmacist to assess the situation and ensure there are no complications that would warrant review by another health practitioner.
   - Listing larger pack sizes in Schedule 3 also provides an opportunity for the pharmacist to ensure that the medicine remains effective and is being used appropriately and that the patient is not doubling up on other paracetamol based products or suffering adverse effects from ibuprofen use.

Conclusion

The availability of an ibuprofen/paracetamol combination product would provide an alternative therapeutic agent for the short-term relief of pain or fever. [redacted] believes that the safety profile of this product is such that listing in a non-prescription schedule of the SUSMP would be appropriate.

However, [redacted] only supports the proposal for the inclusion of small pack sizes of a combination product in Schedule 2 of the SUSMP. [redacted] believes larger pack sizes would be more appropriately managed in consultation with the pharmacist to ensure safe and appropriate use and to minimise any risk of misadventure due to misuse or unintentional paracetamol overdosage.

Reference Sources:

[1] AF Merry, RD Gibbs, J Edwards et al; Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial

[2] National Coordinating Committee on Therapeutic Goods Scheduling Policy Framework for Medicines and Chemicals – 1 July 2010; www.tga.gov.au

[3] HF Miranda, MM Puig, JV Prieto, G Pinardi; Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain; Pain 121 (2006) 22-28; www.elsevier.com/locate/pain

[4] AF Merry, RD Gibbs, J Edwards et al; Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial

[5] MIMS Online January 2011; Drug Interactions: paracetamol vs ethanol; www.mimsonline.com.au

[6] http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm239955.htm

XXXXX
January 14th 2010

The Secretary,
National Drugs and Poisons Schedule Committee (NDPSC),
PO Box 9848,
Canberra
ACT 2601

Dear Secretariat,

Re: Application for Appendix H listing of pantoprazole 20mg for up to 14 days use

Proton Pump Inhibitors (PPIs) are well established as the gold-standard therapy for the management of oesophageal reflux. Pantoprazole, like other PPIs, has an excellent safety profile, and its non-prescription availability poses no increased risk to patients who manage heartburn with over-the-counter medications.

I previously submitted a letter supporting the Appendix H listing for pantoprazole, at the 55th NDPSC meeting held in February 2009. One of the primary reasons for supporting this scheduling change was based on the pharmacy education programme implemented by Nycomed, the marketer of pantoprazole in Australia. This education programme not only guided pharmacists on the appropriate use of the product but it also had a clear mechanism for referring patients to a doctor for medical review, an initiative that is not promoted by the alternative non-prescription treatment options.

A year on from my initial letter of support, I am pleased to see that the clinical audit conducted in pharmacy[1] has demonstrated that this approach has been adopted and pharmacists are playing an important triage role in the management of this common condition.

I continue to support the inclusion of pantoprazole on Appendix H as advertising of this product will encourage more people to discuss their heartburn and reflux symptoms with a healthcare professional and this can only lead to an improvement in its management.

Yours sincerely

XXXXX

XXXXX

References: Scius Solutions, Somac Heartburn Relief: Pharmacy validation research. Clinical study report NY517. 24/09/2009

2.2.2 Pantoprazole - submission 2/10

XXXXX

13th January 2011

The Secretary,
Scheduling Secretariat

Dear Sir,

Re: Meeting of the Advisory Committee on Medicines Scheduling – 23 February 2011: Pertaining to the inclusion of pantoprazole 20 mg in Appendix H of the SUSDP.

I am writing to confirm my continued support for pantoprazole 20 mg to be listed in Appendix H enabling direct to consumer advertising.

The purpose of Schedule 3 is "*to allow effective medicines or preparations that require professional advice on use to be made available to the public from a pharmacist without a prescription.*" In considering whether a Pharmacist Only Medicine is able to be advertised and thus listed in Appendix H the following is to be considered:

- *The potential public health benefit.*
- *The likelihood of advertising of the substance leading to inappropriate patterns of medication use;*
- *Whether the application may result in the advertising of goods for an indication other than those included in the Australian Register of Therapeutic Goods*
- *The responsibility of pharmacists to be actively involved in the supply of substance(s) included in Schedule 3 of SUSDP;*
- *Available consumer medicine information;*
- *The level of patient education necessary to ensure correct use;*
- *The desire of consumers to manage their own medication;*

XXXXX

This study provides specific Australian pharmacy data that supports the case for pantoprazole 20mg to be listed in Appendix H.

Public health benefit	In XXXXX audit, half (56%) of customers who consulted with the pharmacist suffered from frequent heartburn for which a PPI (such as pantoprazole) is the most suitable therapy. One in twenty pharmacist consultations resulted in a GP referral to investigate atypical symptoms. Hence a public health benefit - namely improvements in the quality use of heartburn medications - was demonstrated by encouraging consumers to speak with the pharmacist.
Would advertising lead to inappropriate usage	XXXXX audit found no evidence to support this. In the vast majority of cases (86%) pharmacist and consumers were in agreement as to whether pantoprazole was an appropriate

	treatment option for the particular customer.
The responsibility of pharmacists to be actively involved in the supply of substance	XXXXX audit confirmed that pharmacists appropriately managed the use of pantoprazole in the Schedule 3 setting. Its use was consistent with established protocols and when atypical symptoms were present referral for medical review occurred. In addition, when heartburn symptoms occurred less frequently or were mild, alternative therapies, such as antacids and histamine-2 receptor antagonists, were recommended.
The level of patient education necessary to ensure correct use	XXXXX audit included an investigation of consumer label comprehension. Consumer comprehension of Somac Heartburn Relief packaging was excellent, with 92% of consumers identifying the correct dosage and 86% correctly determining the maximum duration of therapy before seeking advice from their doctor.

In summary, I believe that this research clearly demonstrates that there is an unquestionable public health benefit for advertising of pantoprazole and request that the Committee lists pantoprazole 20mg in Appendix H.

Yours sincerely,

XXXXX

XXXXX

[redacted]

21 January 2011

2.2.2 Pantoprazole - submission 3/10

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Email: SMP@health.gov.au

Invitation for public comment – ACMS meeting 22 February 2011

1.1 Pantoprazole
Proposal to create a new entry for Pantoprazole in Appendix H

[redacted] appreciates the opportunity to provide comment in relation to this issue. We wish to address relevant matters under section 52E of the Therapeutic Goods Act 1989 as these apply to the substance mentioned above: (a) risks and benefits; (b) substance purpose; (c) toxicity; (e) potential for abuse.

Introduction

The current Schedule 3 entry for Pantoprazole is as follows:

> *"… in oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply."*

The question for the [redacted] is whether the availability of such a product ought to be brought to the attention of consumers through advertising directed to them.

For the reasons outlined below, [redacted] contends that consumers ought to be made aware of such products and supports the inclusion of Pantoprazole in Appendix H.

February 2010 NDPSC meeting

A review of the Record of Reasons from the February 2010 NDPSC meeting indicates the following relevant points.

The applicant indicated that:

- Pantoprazole's favourable safety profile had been demonstrated through extensive worldwide data (which included data on OTC use).
- Heartburn and acid reflux were common conditions, with the majority of sufferers self-medicating.

[redacted]

- If consumers were self-treating with antacids and H2RA's, without the advice of a healthcare professional, they were missing an opportunity to consider a more effective and more appropriate treatment such as Pantoprazole.
- Educational tools and treatment protocols were available to pharmacists and were being used appropriately.
- There was over 15 months of experience with Pantoprazole in Australia.
- There were convincing arguments for public health benefits and no negative impacts.

The evaluation report indicated that:

- Pantoprazole ought to be included in Appendix H.
- Educational materials provided to pharmacists were of a generally high standard.
- Audit data showed that pharmacists were willing to provide considered advice.
- There was under usage of Pantoprazole in comparison with less efficacious products.
- There was a reasonable argument that there were public health benefits to be gained by allowing direct-to-consumer advertising (benefits such as earlier identification of consumers who required medical attention and more effective treatment for consumers who are suitable for self-medication).
- Advertising would result in a greater proportion of consumers with heartburn seeking professional advice.

NCCTG Guidelines on Schedule 3 Advertising

In order to assist applicants, the NCCTG has published guidelines describing the process for determining whether a substance in Schedule 3 may be advertised[1].

It is [redacted] position that these guidelines have been met in relation to Pantoprazole and offers the following comments in relation to each of the guidelines:

Potential public benefit

As noted above in relation to the February 2010 meeting, the applicant argued that advertising would provide public benefit and the evaluator agreed with this assessment (as did some members of the Committee). [redacted] contends that advertising will prompt consumers to seek advice from a pharmacist and that such advice may result in more effective treatment or earlier identification of consumers who require medical intervention.

Additionally, [redacted] suggests that inclusion in Appendix H will provide a public benefit through potential reduction in unnecessary visits to GP's. Any such reduction would be strengthening the role of Schedule 3 medicines in removing the need for a prescription in order to access them. Where a consumer becomes aware of Pantoprazole through advertising and obtains the product after a consultation with the pharmacist, then he or she will be in a similar position as if they were provided with a prescription from their GP. However, they will have obtained the product (and the advice) without occupying the GP's time. This reduction in the burden on GP's will be of public benefit.

Further, while Pantoprazole remains in Schedule 3, the pharmacist will continue to act as a final safeguard between the consumer and the product. No matter what the effect of advertising, the consumer cannot purchase the product except with the intervention of the pharmacist. This ought to be kept in mind when weighing the benefits of inclusion in Appendix H against any potential risk that advertising may inappropriately influence demand.

[1] http://www.tga.gov.au/ndpsc/ndpsc3a.htm

Likelihood of advertising leading to inappropriate patterns of use

[redacted] has seen no evidence and can envisage no arguments to suggest that the advertising of Schedule 3 Pantoprazole products will result in inappropriate use.

The wider regulatory system

All advertising to consumers must comply with the *Therapeutic Goods Act*, the *Therapeutic Goods Regulations* and the Therapeutic Goods Advertising Code. Inclusion of Pantoprazole in Appendix H will not affect the various requirements imposed by these instruments.

Among other things, any Pantoprazole advertising to consumers must be consistent with the registered indications, must comply with a range of general principles, must comply with the requirements for prohibited and restricted representations and must contain certain information (including the statement "Your Pharmacist's Advice Is Required").

The responsibility of Pharmacists to be involved

Educational tools and treatment protocols have been prepared in relation to Pantoprazole in order to ensure that pharmacists are able to provide appropriate professional advice.

Availability of Consumer Medicine Information (CMI)

CMI is available in relation to Pantoprazole (e.g. SOMAC Heartburn Relief).

Desire for consumers to manage their own medication

In general, there is no doubting the interest that consumers have in accessing medical and pharmaceutical information and in taking control of their medication and treatment.

In particular, the growth of the gastrointestinal category in supermarket products shows the willingness of consumers in this category to manage their own medication.

[redacted] view all of the above guidelines have been sufficiently addressed.

52E(1)(a) Risks and benefits

The favourable safety profile of Pantoprazole has been demonstrated worldwide in both prescription and over-the-counter settings.

Advertising will prompt consumers to seek advice from a pharmacist and such advice may result in more effective treatment or earlier identification of consumers who require medical intervention.

Advertising has the potential to reduce the burden on GP's and to better inform consumers.

High quality educational tools and treatment protocols have been prepared by [redacted] These tools will ensure that pharmacists provide appropriate professional advice to consumers responding to any advertising.

Any advertising will have to comply with a range of regulatory requirements. Even if advertising inappropriately influenced demand, the pharmacist must be involved in the purchase of the product.

52E(1)(b) Purpose

The purpose of the product is for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease. This purpose is capable of being communicated to consumers via advertising.

52E(1)(c) Toxicity

Pantoprazole has a well documented safety profile.

52E(1)(e) Potential for abuse

[redacted] unaware of any evidence that Pantoprazole is associated with dependence, abuse or illicit use.

Summary

Pantoprazole ought to be included in Appendix H, for the various reasons outlined above.

We believe that the safety profile; history of safe use; indication for short-term use; the ability of pharmacists to provide professional advice to ensure the quality use of medicines; the preparation of pharmacy through education and information provision; and, the potential public health benefit resulting from increased awareness of all available treatments all combine to provide a sound justification for products containing this substance (as Schedule 3) to be advertised.

We trust that the Committee will consider the merit of this submission for the inclusion of Pantoprazole in Appendix H in terms of the efficacy and safety of this substance compared to others that are currently available and able to be advertised. We believe that consumers stand to benefit immensely through awareness of the options available to them, supported through mandatory intervention by pharmacists.

We look forward to hearing the outcomes of the Committee's deliberations on this issue.

Yours faithfully,

[redacted]

2.2.2 Pantoprazole - submission 4/10

[redacted]

18th January 2011

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Dear Sir,

Re: Public Submission – under Reg. 42ZCZK of the Therapeutic Goods Regulations 1990; 22nd February Meeting of the ACMS.

We refer to the pre-February 2011 Scheduling Meeting notice and wish to comment specifically on the application for Appendix H listing of pantoprazole. The comments below address a matter mentioned in section 52E of the Therapeutic Goods Act.

[redacted] of rabeprazole [redacted] a proton pump inhibitor which is Schedule 3 in oral preparations of 10mg or less of rabeprazole, in pack sizes of not more than 14 days supply. An application for Appendix H listing of rabeprazole [redacted] and may be on the agenda for the June meeting of the ACMS.

[redacted] believes that a consistent approach should be applied to Appendix H listing for S3 rabeprazole and pantoprazole and that there are significant potential benefits in terms of increased awareness of more efficacious treatment options. The risks of misuse are low and the safety of PPIs as a group is equivalent to that of H2RAs, which are unscheduled and are advertised freely.

Rabeprazole and pantoprazole are both PPIs and can be considered to be equivalent in efficacy, though there may be some minor differences in pharmacokinetic profile and potency. Nonetheless, the equivalence has already been acknowledged by the NDPSC and both have been allowed an S3 scheduling in Australia. We therefore believe that both pantoprazole and rabeprazole should be viewed similarly in terms of Appendix H approval to advertise directly to the public

Pantoprazole (Somac) has been marketed since November 2008. Rabeprazole (Pariet 10) will be launched in January 2010. Availability in itself does not equate to public or consumer awareness, and many reflux sufferers may be unaware that pharmacists can recommend a PPI for frequent heartburn associated with GORD. Some of these consumers are chronic users of antacids, which have very low efficacy, and H2 receptor

[redacted]

antagonists (H2RAs). Many of these consumers would benefit from a course of PPI treatment but are unaware of its availability. Increased consumer awareness of a more effective treatment such as a PPI would be beneficial to this group of consumers.

Use of a short course of PPIs is cost effective and provides cost benefits and improvement to quality of life for GORD sufferers. Untreated GORD is a significant cause of absenteeism and treatment of GORD with on-demand rabeprazole has been found to improve patients' quality of life and psychological wellbeing.

There is little risk to the community by advertising PPIs for symptomatic treatment of GORD. OTC PPIs are available as 14 day treatment packs and due to the short length of a course of treatment there is very little risk that serious symptoms will be masked or that diagnosis of serious conditions will be delayed. Pharmacists will continue to have control of the product at the point of sale and will refer any patients with "alarm" symptoms. Pharmacists have guidelines for supply of PPIs, and due to the length of time that pantoprazole has been marketed they are by now very familiar with the indications and contraindications and when to refer. Thus the potential inappropriate use for non-GORD indications is very low.

[redacted] believes that a consistent approach should be applied to Appendix H listing for S3 rabeprazole and pantoprazole and that there are significant potential benefits in terms of increased awareness of a more efficacious treatment option. The risks of misuse are low and the safety of PPIs as a group is equivalent to that of H2RAs, which are unscheduled and are advertised freely.

For the purposes of [redacted] to the ACMS for Appendix H approval of rabeprazole, [redacted] sought the opinions of specialist gastroenterologists as to the appropriateness of direct to consumer advertising and the equivalence of PPIs in general. Please see attached the letter from [redacted]. In the opinion of [redacted], there is little risk of harm from direct to consumer advertising of PPIs.

Equivalence of rabeprazole and pantoprazole

[redacted] believes that rabeprazole and pantoprazole should be considered as a group in relation to Appendix H listing. The differences between these OTC PPIs are minor and clinically the two medicines can be considered the same even though there may be minor pharmacokinetic differences.

A meta-analysis published in 2003[1] stated that there is no significant difference between equivalent doses of PPIs. This meta- analysis identified all double blind randomized controlled trials comparing one PPI with another for the treatment of GERD (GORD), using endoscopic healing as the reference standard for treatment success. A total of 16 studies for treatment of GERD (GORD) were identified with most lasting 4 weeks. This is

not the OTC treatment duration, however it illustrates that even at what would normally be prescription dose and duration, the differences between PPIs are not clinically significant.

There are many other papers that have been published since then which describe small differences in various other pharmacodynamic and pharmacokinetic parameters among PPIs. The decision to prescribe one PPI over another usually rests on the physician's or pharmacist's interpretation of the clinical importance of the generally small differences among the PPIs.

In terms of drug interactions, both pantoprazole and rabeprazole have a low potential for significant drug interactions other than those attributable to the group effect of all PPIs. Rabeprazole also shows a low potential for significant pharmacokinetic interactions. The TGA / MEC required the labeling of Pariet 10 to show the same warnings as OTC Somac (pantoprazole). The labeling and CMI provide information about interactions, and pharmacists can advise patients who have significant co-morbidities or are on other medications that may pose an interaction risk. These patients should be under the care of a physician.

At the February 2010 meeting, the NDPSC rejected an application for Appendix H listing of pantoprazole; at the same meeting two other PPIs, lansoprazole and omeprazole were scheduled similarly to rabeprazole & pantoprazole. In both cases it was agreed that a consistent approach for all PPIs should be undertaken in relation to Appendix H listing (p. 187 of Record of Reasons for February 2010 meeting).

[redacted] therefore believes that a class approach should be taken regarding Appendix H listing, since the clinical differences between rabeprazole and pantoprazole are not significant.

Please contact me should you require any further clarification.

Yours sincerely

[redacted]

[redacted]

Reference:

1. Klok RM, Postma MJ, Van Hout BA, Brouwers JRBJ. Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use. *Aliment Pharmacol Ther 2003; 17: 1237-1245*

Aliment Pharmacol Ther 2003; 17: 1237–1245.

doi: 10.1046/j.0269-2813.2003.01562.x

Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use

R. M. KLOK*, M. J. POSTMA*, B. A. VAN HOUT† & J. R. B. J. BROUWERS*

**Groningen University Institute for Drug Exploration/University of Groningen Research Institute of Pharmacy (GUIDE/GRIP), Department of Social Pharmacy, Pharmaco-epidemiology and Pharmacotherapy, Groningen, The Netherlands; †Dutch Center for Health Economics and System Science, Capelle aan de Ijssel, The Netherlands*

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SUMMARY

Background: Proton pump inhibitors have a prominent role in the management of acid-related diseases. Controlling expenses on proton pump inhibitors would yield great economic benefits for Dutch health care.

Aim: To investigate whether clinical differences in proton pump inhibitors exist.

Methods: We searched Medline, EMBASE and the Cochrane Library. We identified papers in English, German, French or Dutch in which two or more proton pump inhibitors were compared under the same clinical conditions in gastro-oesophageal reflux disease, peptic ulcer disease or *Helicobacter pylori* eradication. The pooled relative risks were calculated using the Mantel–Haenszel method.

Results: Two significant differences were found in the proton pump inhibitors compared. In gastro-oesophageal reflux disease, esomeprazole 40 mg was superior to omeprazole 20 mg (relative risk, 1.18; 95% confidence interval, 1.14–1.23). In peptic ulcer disease, pantoprazole 40 mg was superior to omeprazole 20 mg (relative risk, 1.07; 95% confidence interval, 1.02–1.13). In *Helicobacter pylori* eradication, no significant differences were found.

Conclusions: Both significant differences found were in favour of the highest dose of proton pump inhibitor on a milligram basis. This indicates that the difference may be dose dependent and not proton pump inhibitor specific. Therefore, when prescribing proton pump inhibitors, arguments other than clinical efficacy, such as those related to pharmaco-economics, may be considered.

INTRODUCTION

Proton pump inhibitors have a prominent role in the management of acid-related diseases. They are the drugs of choice in gastro-oesophageal reflux disease (GERD), peptic ulcer disease, in combination with one or more antibiotics in the eradication of *Helicobacter pylori* and as a gastric protective agent when using non-steroidal anti-inflammatory drugs. Before the introduction of proton pump inhibitors, histamine-2-receptor antagonists and antacids were used in acid-related disorders. Proton pump inhibitors have been shown to be more effective than histamine-2-receptor antagonists and antacids in controlling acid-related diseases.[1, 2]

In The Netherlands, proton pump inhibitors comprised 66% of the prescriptions and 83% of the drug costs in the acid suppressor group in the year 2000, whereas histamine-2-receptor antagonists were responsible for 32% of the prescriptions and 17% of the drug costs in the same year.[3] In the year 2000, proton pump inhibitors were responsible for almost 10% of the total drug costs in community pharmacy in The Netherlands.[4] This indicates that controlling the expenses on

Correspondence to: Professor J. R. B. J. Brouwers, Groningen University Institute for Drug Exploration/University of Groningen Research Institute of Pharmacy (GUIDE/GRIP), Department of Social Pharmacy, Pharmaco-epidemiology and Pharmacotherapy, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.
E-mail: J.R.B.J.Brouwers@farm.rug.nl

proton pump inhibitors would yield great economic benefits for Dutch health care.

Choosing a proton pump inhibitor can be based on different considerations. The cost, side-effect profile and possible interactions are some of the considerations on which the choice of a proton pump inhibitor can be based. These considerations are important, but only decisive when there is no difference in clinical efficacy of the proton pump inhibitors used. In this study, we analysed randomized controlled trials in which two or more proton pump inhibitors were compared in the short-term management (4 weeks) of GERD, peptic ulcer disease or the eradication of *H. pylori*.

METHODS

Justification

We searched Medline, EMBASE and the Cochrane Library for meta-analyses concerning the efficacy of proton pump inhibitors in short-term treatment. We found several papers comparing one or more proton pump inhibitors with histamine-2-receptor antagonists, and also a recent paper comparing different proton pump inhibitors with omeprazole 20 mg in the acute treatment of reflux oesophagitis.[5] None of the papers found compared all proton pump inhibitors in all dosages in the short-term treatment of GERD, peptic ulcer disease and/or *H. pylori* eradication. As we extended this full spectrum, we believe that our endeavour in this meta-analysis is justified.

Study selection

We searched Medline (1985–2002), EMBASE (1985–2002) and the Cochrane Library (whole period) using the following keywords: omeprazol(e), pantoprazol(e), lansoprazol(e), lanzoprazol(e), rabeprazol(e), esomeprazol(e), GERD, ulcer, *H. pylori*, reflux, with the language restriction English, Dutch, German or French. Abstracts from (poster) presentations at symposia were not included in the search. The studies found were further selected using the following criteria.

(a) A study should present new and original work.
(b) A study should compare two or more proton pump inhibitors under the same clinical conditions (for example, same severity of disease, same dosing scheme, etc.).
(c) Only studies concerning GERD, peptic ulcer disease or *H. pylori* eradication were included, as these reflect the main areas for proton pump inhibitor prescription.
(d) The studies had to be randomized prospective trials.
(e) Efficacy evaluation for GERD and peptic ulcer disease should be performed after 4 weeks of treatment; other time periods of evaluation were excluded.
(f) The presence of GERD and peptic ulcer disease (post- and pre-treatment) should be determined endoscopically.
(g) The detection of *H. pylori* (post- and pre-treatment) should be by urea breath test or endoscopy.
(h) The duration of *H. pylori* therapy should be between 7 and 14 days; studies with other regimen durations were excluded.
(i) The end-point in studies concerning *H. pylori* eradication should be the eradication of *H. pylori*; studies only concerning symptom improvement were excluded.
(j) Studies concerning specific patient groups, such as the elderly, children or mentally disabled persons, were excluded.
(k) Studies of pharmacokinetics, pharmacodynamics or pH measurement were excluded.

The application of these criteria resulted in a final selection of 41 studies.[6–46] Of these studies, 16 considered GERD,[6–21] nine considered peptic ulcer disease[22–30] and 16 considered *H. pylori* eradication.[31–46]

Data extraction and statistical analyses

The information retrieved covered the proton pump inhibitor used, numbers of individuals treated, disease treated and success rate. The success rate was defined as an endoscopically determined cure for GERD and peptic ulcer disease or the assessment of the absence of *H. pylori* after eradication. For each study, the relative risk (RR) of the proton pump inhibitors compared was calculated. Two independent researchers (BAvH and RMK) performed the data extraction and analysis. In the case of disagreement, a third researcher was consulted (JRBJB).

Where possible, the results were pooled using the Mantel–Haenszel method.[47, 48] In this method, the weight given to the studies was based only on the number of patients in the study.

Potential problems with meta-analysis

When conducting a meta-analysis, there are potential problems and sources of bias. One of the main problems in a meta-analysis is publication bias. Studies with unexpected or spectacular results are more likely to be published than studies with unattractive results. In this case, publication bias is probably of little importance,

Table 1. Randomized double-blind studies comparing the efficacy after 4 weeks of treatment of different proton pump inhibitors in gastro-oesophageal reflux disease

Reference	Dose	*n*	Success*	Failure	CI − 95%	RR	CI + 95%
6	P40	103	81	22	0.73	0.99	1.35
	O20	105	83	22			
7	P40	170	126	44	0.71	0.95	1.28
	O20	86	67	19			
8	P40	10	3	7	0.09	0.33	1.23
	O20	10	9	1			
9	P40	60	45	15	0.70	1.07	1.63
	O20	60	42	18			
Pooled results for P40/O20[6–9]					0.88	0.97	1.06
8	L30	10	2	8	0.05	0.22	1.03
	O20	10	9	1			
10	L30	300	186	114	0.89	1.10	1.35
	O20	304	172	132			
11	L30	421	335	86	0.86	1.00	1.16
	O20	431	343	88			
12	L30	113	71	42	0.70	0.96	1.34
	O20	112	73	39			
13	L30	58	47	11	0.73	1.09	1.64
	O20	62	46	16			
14	L30	30	21	9	0.57	1.05	1.94
	O20	30	20	10			
Pooled results for L30/O20[8, 10–14]					0.96	1.02	1.08
15	R20	100	81	19	0.73	1.00	1.35
	O20	102	83	19			
16	R20	104	92	12	0.73	0.97	1.29
	O20	103	94	9			
Pooled results for R20/O20[15, 16]					0.91	0.98	1.06
17	E40	654	496	158	1.03	1.17	1.33
	O20	650	421	229			
18	E40	1216	993	223	1.08	1.19	1.30
	O20	1209	831	378			
Pooled results for E40/O20[17, 18]					1.14	1.18	1.23
11	L15	218	157	61	0.75	0.90	1.09
	O20	431	343	88			
16	R10	103	88	15	0.70	0.94	1.25
	O20	103	94	9			
17	E20	656	462	194	0.95	1.09	1.24
	O20	650	421	229			
19	P20	166	128	38	0.74	0.95	1.21
	O20	161	131	30			
20	L30	104	91	13	0.81	1.09	1.46
	O40	103	83	20			
21	L30	235	188	47	0.81	0.99	1.21
	P40	226	183	43			

CI, confidence interval; E, esomeprazole; L, lansoprazole; O, omeprazole; P, pantoprazole; R, rabeprazole; RR, relative risk.
* Success is endoscopically healed gastro-oesophageal reflux disease.

Table 2. Randomized double-blind studies comparing the efficacy after 4 weeks of treatment of different proton pump inhibitors in ulcer healing

Reference	Dose	*n*	Success*	Failure	CI − 95%	RR	CI + 95%
26	P40	124	118	6	0.83	1.07	1.38
	O20	131	117	14			
27	P40	146	128	18	0.83	1.14	1.56
	O20	73	56	17			
28	P40	193	178	15	0.80	1.03	1.34
	O20	93	83	10			
Pooled results for P40/O20[26–28]					1.02	1.07	1.13
23	L30	73	66	7	0.73	1.04	1.46
	O20	71	62	9			
24	L30	57	51	6	0.72	1.07	1.60
	O20	54	45	9			
25	L30	128	125	3	0.78	1.01	1.30
	O20	121	117	4			
Pooled results for L30/O20[23–25]					0.98	1.03	1.08
29	R20	102	100	2	0.79	1.05	1.39
	O20	103	96	7			
30	R20	113	103	10	0.76	1.00	1.31
	O20	114	104	10			
Pooled results for R20/O20[29, 30]					0.97	1.02	1.08
22	L30	164	154	10	0.73	0.96	1.27
	O40	79	77	2			

CI, confidence interval; L, lansoprazole; O, omeprazole; P, pantoprazole; R, rabeprazole; RR, relative risk.
* Success is ulcer healing.

because the clinical efficacy of proton pump inhibitors is an important subject for decision makers and clinicians.

Another problem in a meta-analysis is selection bias. Selection bias is introduced when not all of the published articles concerning the subject are selected. Through selection, key publications can be missed and the pooled result can be flawed. In this case, selection bias is a problem, because not all languages and only full-text articles were selected. The impact of this bias is not clear. In addition, there are obviously less studies concerning the newer drugs (rabeprazole and esomeprazole).

RESULTS

When comparing the different proton pump inhibitors in the treatment of GERD, one statistically significant result in the pooled RR was found. After 4 weeks, esomeprazole 40 mg was shown to be superior to omeprazole 20 mg in endoscopic healing [RR, 1.18; 95% confidence interval (CI), 1.14–1.23). In all the other comparisons, no significant differences were found (Table 1).

When comparing the different proton pump inhibitors in the treatment of peptic ulcer disease, one significant difference was found in the pooled RR. After 4 weeks, pantoprazole 40 mg was superior to omeprazole 20 mg in ulcer healing (RR, 1.07; 95% CI, 1.02–1.13). All other comparisons showed no significant difference (Table 2).

In the 16 studies concerning *H. pylori* eradication, no significant differences were found. When pooling the results, all 95% CIs included RR = 1 (Table 3).

DISCUSSION

As shown in the individual analyses, esomeprazole 40 mg was found to be superior to omeprazole 20 mg in GERD healing in the pooled analysis. This superiority is not surprising, because esomeprazole is the enantiomer of omeprazole, and the active compound is the achiral cyclic sulphenamide. Comparing 40 mg of esomeprazole with 20 mg of omeprazole would be more or less the same as comparing double the dose of omeprazole.[49] The advantage of chirally pure

Table 3. Randomized double-blind studies comparing the efficacy of different proton pump inhibitors in *Helicobacter pylori* eradication in the same regimens

Reference	Dose	*n*	Success*	Failure	CI − 95%	RR	CI + 95%
31	L60AM†	56	41	15	0.58	0.86	1.29
	O40AM	66	56	10			
32	L60AC†	93	68	25	0.63	0.88	1.22
	O40AC†	90	75	15			
33	L60AC†	186	134	52	0.90	1.17	1.51
	O40AC	170	105	65			
34	L60AC†	74	62	12	0.69	0.98	1.39
	O40AC	75	64	11			
35	L60A‡	23	9	14	0.47	1.17	2.96
	O40A‡	27	9	18			
Pooled results for L60/040[31–35]				0.95	1.05	1.15	
36	L30N‡	26	20	6	0.61	1.21	2.39
	O40N	22	14	8			
37	L30AC†	73	60	13	0.72	1.03	1.47
	O40AC	75	60	15			
Pooled results for L30/040[36, 37]				0.92	1.06	1.23	
34	R40AC†	72	63	9	0.74	1.04	1.48
	L60AC	74	62	12			
38	R40AC†	104	89	15	0.77	1.03	1.39
	L60AC	104	86	18			
Pooled results for R40/L60[34, 38]				0.95	1.04	1.13	
39	R20A‡	101	63	38	0.67	0.94	1.33
	O40A	98	65	33			
40	R20AC†	58	51	7	0.72	1.07	1.59
	O40AC†	57	47	10			
Pooled results for R20/040[39, 40]				0.87	0.99	1.14	
34	R40AC†	72	63	9	0.72	1.03	1.45
	O40AC	75	64	11			
46	R40AC†	78	65	9	0.73	1.02	1.43
	O40AC	86	70	11			
Pooled results for R40/040[34, 46]				0.93	1.02	1.13	
41	P40CM†	25	25	0	0.64	1.14	2.02
	O40CM†	25	22	3			
42	P40AC§	79	66	13	0.64	0.89	1.23
	O40AC	84	79	5			
Pooled results for P40/040[41, 42]				0.86	0.94	1.03	
32	P80AC†	95	73	22	0.67	0.92	1.27
	O40AC†	90	75	15			
42	P80AC§	80	75	5	0.73	1.00	1.37
	O40AC	84	79	5			
Pooled results for P80/040[32, 42]				0.88	0.96	1.04	
43	E40AC†	204	183	21	0.83	1.02	1.26
	O40AC	196	172	24			
44	E40AC†	214	184	30	0.80	0.98	1.20
	O40AC	219	192	27			

esomeprazole compared with omeprazole is its more predictive and linear kinetics. The impact of this advantage for clinical practice is not yet clear. In all other comparisons concerning GERD, no significant differences were found in the proton pump inhibitors compared.

Table 3. Continued

Reference	Dose	*n*	Success*	Failure	CI – 95%	RR	CI + 95%
Pooled results for E40/O40[43, 44]				0.90	1.00	1.11	
37	L30AC†	73	60	13	0.76	1.10	1.57
	O20AC	76	57	19			
45	L30A§	14	4	10	0.17	0.62	2.19
	P40A§	13	6	7			

A, amoxicillin; C, clarithromycin; CI, confidence interval; E, esomeprazole; L, lansoprazole; M, metronidazole; N, norfloxacin; O, omeprazole; P, pantoprazole; R, rabeprazole; RR, relative risk.
* Success is no *Helicobacter pylori* present.
† One week of therapy.
‡ Two weeks of therapy.
§ Ten days of therapy.

In ulcer healing, 40 mg of pantoprazole was shown to be superior to 20 mg of omeprazole. This shows that it is not necessary to double the dose of pantoprazole compared with omeprazole in order to obtain the same results. The other comparisons of the proton pump inhibitors did not yield significant differences.

In the eradication of *H. pylori*, no significant differences were found between the proton pump inhibitors used in the eradication regimens. In the eradication of *H. pylori*, all proton pump inhibitors have a beneficial effect and the failure of eradication is mainly due to antibiotic resistance.[50] Therefore, in clinical practice, small differences in proton pump inhibitor efficacy are probably of limited importance, with antibiotic resistance presenting the major impact. In order to determine whether there are differences in the proton pump inhibitors used, large trials should be designed including a correction for the effect of antibiotic resistance.

As significant differences were found only in two pooled results in which a higher dose of proton pump inhibitor was used for comparison, the differences found are probably dose dependent and not proton pump inhibitor specific. As expected, most comparative studies compared the first available proton pump inhibitor, omeprazole, with another proton pump inhibitor. For a better comparison of all proton pump inhibitors, randomized clinical trials are needed in which comparisons between three or more different proton pump inhibitors are made.

In this study, no account was taken of the potential effects and differences of long-term proton pump inhibitor use. However, studies comparing different proton pump inhibitors over a longer period of time have not shown significant differences in safety and efficacy between the proton pump inhibitors studied.[51–54]

No economic data were considered in this study. However, when all proton pump inhibitors are clinically equal, the drug of choice could be that which is least costly on a daily dose basis. In The Netherlands, the prices of proton pump inhibitors for 1 month, based on the 'defined daily dose',[55] are €41.76 for esomeprazole 20 mg, €42.96 for lansoprazole 30 mg, €43.96 for omeprazole 20 mg, €42.06 for pantoprazole 40 mg and €37.89 for rabeprazole 20 mg.[56] The costs for rabeprazole on a 'defined daily dose' basis are almost 14% less than those for omeprazole. As omeprazole has a market share of approximately 90% in The Netherlands, switching to rabeprazole could save up to €30 million. These drug prices were taken before generic omeprazole was available on the Dutch market; the introduction of generic omeprazole may have already resulted in a saving of €15 million.[57] In a recent review, Krömer *et al.* suggested that the optimal dose in acute peptic ulcer disease and moderate to severe GERD was 30–40 mg for omeprazole, lansoprazole and pantoprazole; for rabeprazole and esomeprazole, there was insufficient information at the time to suggest an optimal dose.[58] For esomeprazole, the dose will probably be the same as for omeprazole, given the presence of the same active compound.[49] When using the costs of the optimal dose, this suggests that the widespread use of pantoprazole and lansoprazole rather than omeprazole and esomeprazole may potentially achieve a cost reduction. The place of rabeprazole is unclear because of a lack of sufficient data.

One of the problems in choosing the least expensive proton pump inhibitor is that changing the medication may be inconvenient for the patient and may result in a lower efficacy of treatment.[59] Therefore, most economic benefits may be expected in patients who are starting treatment.

In conclusion, all proton pump inhibitors appear to be clinically comparable, and the clinical choice may be based on other factors, such as pharmaco-economic considerations.

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[redacted]

9th December 2010

[redacted]

APPENDIX H LISTING FOR PROTON PUMP INHIBITORS (PPI's)

IN THE TREATMENT OF GORD

[redacted] two community surveys over the past decade relating to gastro-oesophageal reflux disease (GORD). This is a frequent problem in the community with two thirds of Australians between 18 and 49 complaining of heartburn (64%) and in 18% this is a frequent problem interfering with their normal activities, either social or work.

As reflux is potentially a life-long problem for the majority of people, even though it may fluctuate in intensity from time to time, there is a great virtue in educating the public about the options available for appropriate treatment.

[redacted] studies indicate that the majority of people self-medicate and do not seek advice from their medical practitioner nor pharmacist regarding long term management.

We believe in an approach that begins with simple therapy and progresses towards more complicated therapy and pharmacists, practitioners and the public need to be aware of this process.

Alarm symptoms such as dysphagia or odynophagia may not always trigger the patient to seek medical advice and they should be aware that these are potential alarm symptoms indicating the probable presence of oesophageal inflammation and ulceration. The use of a treatment algorithm for pharmacies

seems to be potentially helpful and it may also identify at an earlier age, some individuals who are at risk from oseophago-gastric cancer. This is an increasing problem in western men and the problem is increased because of family history or the endoscopic identification of Barrett's oesophagus.

We would certainly favour the identification of any oesophageal lesion before beginning long term PPI therapy, but if these medications are available OTC, Rabeprazole/Pantoprazole without significant benefit unless taken continually, this too is a trigger for referral to a medical practitioner for long term advice.

This consultation also allows an opportunity to discuss lifestyle measures such as obesity, alcohol, smoking and other dietary ingredient such as fat and caffeine that might precipitate symptoms and be important in long term management.

[redacted]there is little risk from an approach from OTC PPI's and there is a significant benefit by having the opportunity to trigger a referral for further advice.

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The Scheduling Secretariat
Advisory Committee in Medicines Scheduling
Canberra
ACT

January 19th 2011

Dear Secretary

Re: Application for Appendix H listing of pantoprazole 20mg for up to 14 days use

I have been asked once again to provide comment on the scheduling of low-dose pantoprazole (20 mg/day for up to 14 days treatment). I did write to the NDPSC one year ago related to this and enclose a copy of that letter. As before, I have not been remunerated for providing this opinion but am willing to do this as I am a gastroenterologist with long experience and expertise in the field.

The previous letter summaries the issues related to Appendix H listing and pantoprazole. Since then, a pharmacy audit commissioned by Nycomed on the management of heartburn in Australia has been published.[1] The results of this audit indicate that overall, pharmacists seem to be implementing the use of non-prescription pantoprazole in an appropriate manner.

Compared with other non-prescription heartburn treatments, pantoprazole 20mg provides consumers with an incremental improvement in efficacy without any apparent compromise in safety. It has been available now over the counter for some time. Therefore, it seems reasonable that as Appendix H listing has been deemed appropriate for other commonly used pharmaceutical agents, that pantoprazole be afforded the same regulatory status as these.

Yours sincerely

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Reference: 1. Bell J, Katelaris PH, Krassas G. An Australian pharmacy audit of the management of heartburn and the role of over the counter proton pump inhibitors. Pharmacist 2010; 29: 526-8.

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The Secretary,
National Drugs and Poisons Schedule Committee (NDPSC),
PO Box 9848,
Canberra
ACT 2601

January 13th 2010

Dear Secretariat

Re: Application for Appendix H listing of pantoprazole 20mg for up to 14 days use

I have been asked to provide comment on the scheduling of low-dose pantoprazole (20 mg/day for up to 14 days treatment). As a gastroenterologist with a long experience and expertise in the use of proton pump inhibitors (PPIs) and XXXXX I willing to do this. I have not been remunerated for providing this opinion.

PPIs are the gold-standard therapy for the management of oesophageal reflux and have an excellent safety profile. The non-prescription availability of PPIs is a natural progression for this well established therapy. These agents are available over the counter in many countries including the USA, European Union countries and in Asia as well as in Australia.

To date, the non-prescription availability of lower dose pantoprazole for short term use has not posed any discernible increase in risk to patients. Concerns regarding masking disease and delaying medical review are the same for non-prescription PPIs as they are for antacids and histamine-2 receptor antagonists which are unscheduled medicines and have been available for a long time. This opinion is reflected and discussed in a recently published clinical review, which XXXXX, [2] (Appendix 1).

The conclusions of this review are applicable to the Australian context and the treatment algorithm described in the paper is comparable to that advised in a recent Australian industry sponsored pharmacy education program.

XXXXX the 2009 pharmacy audit commissioned by Nycomed on the management of heartburn in Australia.[3] The results of this audit indicate that overall, pharmacists seem to be implementing the use of non-prescription pantoprazole in an appropriate manner. The pharmacists audited are managing consumers presenting with heartburn in a way that is consistent with the treatment algorithm developed for non-prescription pantoprazole. It is reassuring to observe that these pharmacists appear to be performing a triaging role and people presenting with alarm symptoms are being referred to a doctor for medical assessment.

Compared with the more widely available non-prescription heartburn treatments, pantoprazole 20mg provides consumers with an incremental improvement in efficacy without any apparent compromise in safety. Therefore, if Appendix H conditions are deemed appropriate for other common pharmaceutical agents, it seems reasonable to afford pantoprazole the same regulatory listing as these.

Yours sincerely

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2.2.2 Pantoprazole - submission 6/10

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The Medicines and Poisons Scheduling Secretariat
Office of Chemical Safety and Environmental Health (MDP 88)
Department of Health and Ageing
GPO Box 9848
Canberra ACT 2600

February 2011 Meeting Advisory Committee on Medicines Scheduling (ACMS)
Pantoprazole-proposal to create a new entry in Appendix H

I wish to lodge a pre-meeting comment (public submission) to the February 2011 meeting of the ACMS in relation to "Pantoprazole - proposal to create a new entry for pantoprazole in Appendix H" so as to allow products containing pantoprazole in Schedule 3 to be advertised to the general public

This matter was considered at the February 2010 meeting of the now disbanded NDPSC. Although the application to allow advertising at that time was supported by a favourable TGA evaluation, that Committee raised a number of concerns in relation to the key issue agreed to by that Committee, namely that whether a significant overall public health benefit would result from advertising.

Of specific concern of the Committee was that listing in Appendix H was not appropriate at that time as it considered that at least twelve months OTC marketing experience in Australia was required so that Australian-specific data could be provided to inform any decision on the appropriateness of an Appendix H listing.

Pantoprazole 20mg as an OTC Schedule 3 product was introduced to the Australian market in September 2008. The product has now been on the Australian market for a further year since the February 2010 meeting of the NDPSC and has thus been on the OTC market for two and a half years. This further period of marketing experience has shown no increase in the occurrence of adverse reactions reported and demonstrates that the Australian use-pattern is for a product with an excellent safety profile.
This Australian experience mirrors the post marketing experience from comparable overseas countries where OTC proton pump inhibitors have been permitted to be advertised to the general public for a number of years (the United Kingdom, the USA, Sweden, Denmark and Norway).

The other specific concern of the Committee was the benefit to public health. The Australian Gut Foundation estimates that 10% of the adults over the age of 18 years experience heartburn at least 2 times a week. This is a significant proportion of the Australian population which the Foundation also has evidence that this group of people self-medicate using products predominately purchased from supermarkets. These people are therefore unlikely to discuss

newer and more effective options with a health professional unless they become aware of the availability of the alternative products.

I believe that advertising within the S3 guidelines will correct this situation and will therefore produce a significant public health benefit through improved health outcomes. This position was supported by the earlier TGA evaluation which stated “the application had provided reasonable argument in favour of its contention that there were potential public health benefits to be gained by direct-to-consumer advertising”.

Most importantly, a regular heartburn sufferer would welcome the fact that an alternative and more effective product was available that would improve their quality of life with the safeguard that there is intervention by a health professional to ensure use of the product is appropriate.

In summary the advertising of OTC pantoprazole within the S3 guidelines is strongly supported.

- Australia now has two and a half years of post-marketing experience with OTC pantoprazole.

- A significant proportion of the population will clearly benefit from OTC pantoprazole if it was made aware of its availability, resulting in improved health outcomes, a clear public health benefit.

- Pharmacists are using the protocols that have been developed by the sponsor and the Pharmaceutical Society of Australia to ensure that only suitable patients will commence treatment and that, if necessary, patients will be referred to a general practitioner. (Australian post marketing experience shows that 5% of consumers were deemed unsuitable for treatment and referred to a general practitioner).

Yours sincerely

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2.2.2 Pantoprazole - submission 7/10

21st January 2011

Attention to: Secretary to the Scheduling Secretariat

RE: The inclusion of pantoprazole 20mg in Appendix H

Dear Sir,

Pharmacist Only Medicines are an important class of medications that give consumers easier access to medications whilst retaining the intervention and review of a healthcare professional.

Pantoprazole has been a Pharmacist Only Medication for more than two years in Australia. This has allowed pharmacists sufficient time to establish pharmacy protocols for the over-the-counter use of this medication.

I support the inclusion of pantoprazole in Appendix H as it will inform heartburn sufferers about alternative treatments for their condition. As the product can only be purchased with the involvement of a pharmacist, the appropriateness of treatment used will improve.

Pharmacists have a professional obligation to recommend the most appropriate treatments for their clients, whether it is an unscheduled medicine, a pharmacist only medicine or no medicine but to seek doctor's advice. As a profession we fulfill this duty-of-care thousands of times each day. The appendix H listing of pantoprazole will create more opportunities for pharmacists to engage with people suffering from heartburn and to improve their care.

I ask Committee to consider my opinion, a view that I believe is consistent with the vast majority of the pharmacy profession. The inclusion of pantoprazole in Appendix H will improve the management of heartburn by enabling pharmacist involvement in this common condition.

Yours faithfully,

XXXXX

[redacted]

19 January 2011

Comments by the [redacted] to the Advisory Committee for Medicines Scheduling – Meeting of 23 February 2011

Proposal

Pantoprazole – proposal to create a new entry for pantoprazole in Appendix H.

[redacted] does not object to the inclusion of pantoprazole in Appendix H of the Standards for the Uniform Scheduling of Medicines and Poisons (SUSMP), noting that such inclusion:

- should be consistent across the spectrum of proton pump inhibitors (PPIs) listed in Schedule 3 of the SUSMP and
- must manage the risk for the potential advertising of related Schedule 4 products containing PPIs.

Contact person:

[redacted]

[redacted]

Introduction

Whilst acknowledging that responsible advertising of Schedule 3 products may have some public benefit by prompting health professional intervention through raising consumer awareness of relevant health conditions and the availability of possible treatments, [redacted] has concerns about consumers requesting specific Schedule 3 products based solely on an advertisement.

Clever product advertisement can significantly influence a consumer's decision on how a particular condition should be managed, making it difficult for pharmacists to effectively meet their professional responsibilities by assessing the appropriateness and safety of a direct product request for a Schedule 3 medicine.

Whilst [redacted] supports direct to consumer advertising that advises consumers with specific conditions to consult their pharmacist, we are reticent to support including Schedule 3 medicines in Appendix H of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), particularly newly approved Schedule 3 listings that have been down-scheduled from Schedule 4. In these instances, [redacted] believes that it is in the public interest for pharmacists to become accustomed to the protocols and responsibilities associated with the non-prescription supply of these medicines before they have to manage direct product requests resulting from advertising campaigns.

Comments

[redacted] has considered the proposal to list pantoprazole in Appendix H of the SUSMP and provides the following comments with consideration given to the guidelines provided in the *Scheduling Policy Framework for Medicines and Chemicals*[1] (Scheduling Framework).

Background

Pantoprazole is a proton pump inhibitor (PPI) for which a 20 mg or less unit strength was listed in Schedule 3 of the SUSMP from 1 May 2008 in packs of not more than 14 days supply for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease.

Since then, other PPIs, including rabeprazole 10 mg or less, omeprazole 20 mg or less and lansoprazole 15 mg or less have also been listed in Schedule 3 of the SUSMP with similar restrictions.

A clinical protocol[2] for the supply of pantoprazole has been developed by the Pharmaceutical Society of Australia (PSA) to assist pharmacists in meeting their professional obligations when supplying it as a Schedule 3 medicine.

1. Is there a need to advertise availability of these Schedule 3 medicines?

Although [redacted] concerns with direct to consumer advertising for Schedule 3 medicines is primarily with pharmacists having to manage inappropriate patient requests, we also acknowledge that there can be some consumer and public benefit. In the instance of pantoprazole and other Schedule 3 PPIs, this includes:

[redacted]

- **Increased consumer awareness of an effective treatment**
  Consumers that suffer with more frequent bouts of heartburn or reflux will be more aware of an effective treatment and may be prompted to seek health professional input.

- **Prompting patients relying on antacids or ranitidine to seek pharmacist advice**
  Many consumers with reflux and upper gastro-intestinal complaints self medicate, often using antacids or H2-receptor antagonists (H2RAs) such as ranitidine, obtained from supermarkets or other general retail outlets. It is important that patients who suffer reflux symptoms and/or who take heartburn or reflux medicines continuously over a long period are reviewed by a health professional.

  Increased awareness of new, effective treatments for heartburn and reflux may prompt consumers who regularly purchase antacids or ranitidine from supermarkets without any review to consult their pharmacist for more information. This would provide their pharmacist with an opportunity to assess and provide more appropriate therapy options and/or lifestyle support, or to refer if required.

2. **Is there concern for irresponsible advertising or adverse public outcomes from any advertising campaigns?**

- [redacted] believes that there is no more concern with the advertising of Schedule 3 PPIs than there is with antacids and H2RAs. Considering the interaction profile of antacids, and the fact that H2RAs are only indicated for the short-term management of reflux symptoms without medical advice, the advertising of Schedule 3 PPIs would actually be in the public interest by raising awareness of other therapies and prompting consultation with a health professional.

- The safety profile of PPIs is reasonable and there is no abuse potential risk to justify restricting direct to consumer advertising of Schedule 3 PPIs.

- [redacted] does not believe there is any significant concern that Schedule 3 PPIs would be irresponsibly advertised or that any advertising would be detrimental to the public. However, PPIs are unusual in that the same medicine is also listed in Schedule 4 of the SUSMP for which direct-to-consumer advertising is banned.

  Should the committee support the listing of pantoprazole and other PPIs within Appendix H of the SUSMP, there should be caveats attached to ensure that there is no advertising, whether accidental or intentional, of related prescription only products. This may be achieved by only permitting the advertising of Schedule 3 products in which the brand name is distinct from that of the Schedule 4 counterpart.

[redacted]

3. **Are pharmacists sufficiently accustomed to protocols and responsibilities associated with the supply of these Schedule 3 medicines?**

- With pantoprazole being available since May 2008 as a Schedule 3 medicine, pharmacists have had ample time to become accustomed to protocols and responsibilities associated with the supply of Schedule 3 PPIs. Although the PSA Protocol[2] is specific for pantoprazole, it can easily be applied to other Schedule 3 PPIs as most of the individual processes and considerations are non-specific.

- There has been concern about a potential interaction between PPIs and the antiplatelet medicine, clopidogrel, which may reduce the effectiveness of clopidogrel and increase a patient's risk to thrombo-embolic events.

  However, the European Medicines Agency (EMA) has recently indicated that the only PPIs concerned are omeprazole and esomeprazole and that there is no solid grounds to extend any warning to other PPIs[3].

  [redacted] also contends that pharmacists are sufficiently experienced in managing such interactions from the prescribed supply of clopidogrel and PPIs and would be quite capable of extending this function to the non-prescription supply of Schedule 3 PPIs. The most important thing would be to ensure that pharmacists have access to current information and guidance to support their clinical judgement, and [redacted] would be pleased to collaborate with sponsors and other professional organisations to facilitate this.

Conclusion

PPIs are safe and effective therapies for the treatment of heartburn and gastro-oesophageal reflux and many consumers who currently self medicate with antacids or H2RAs may benefit from being aware of the availability of superior, alternative therapies and consulting a health professional.

[redacted] is aware that the National Drugs and Poisons Schedule Committee (NDPSC) has previously considered including pantoprazole and other PPIs in Appendix H and decided against this proposal. However, circumstances have changed in the short time since then with one of the main risks identified (the potential interaction with clopidogrel) no longer being of such concern. [redacted] contends that pharmacists are sufficiently capable of mitigating any remaining risk in the same manner that they do when dispensing PPIs and clopidogrel from a prescription.

[redacted] does not object to including pantoprazole in Appendix H of the SUSMP with caveats attached to ensure that there is no advertising of the prescription only forms of the medicine. We also note that should the inclusion of pantoprazole within Appendix H of the SUSMP be supported, this decision should be consistent across the spectrum of Schedule 3 PPIs.

[redacted]

Reference Sources:

[1] National Coordinating Committee on Therapeutic Goods Scheduling Policy Framework for Medicines and Chemicals – 1 July 2010; www.tga.gov.au
[2] Provision of pantoprazole as a Pharmacist only medicine for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease; PSA; September 2008; www.psa.org.au
[3] Interaction between clopidogrel and proton-pump inhibitors; EMA/1794948/2010; 17 March 2010; http://www.ema.europa.eu/humandocs/PDFs/EPAR/Plavix/17494810en.pdf

[redacted]

2.2.2 Pantoprazole - submission 9/10

[redacted]

13 January 2011

Advisory Committee on Medicines Scheduling
Email: smp@health.gov.au

Dear Secretariat,

Re: Appendix H listing of pantoprazole 20mg

I am writing to express my continued support for the Appendix H listing of pantoprazole 20mg for up to 14 days use.

It is well established that pantoprazole has an excellent safety profile, equivalent to other over-the-counter heartburn pharmacotherapies and is a more effective.

As pantoprazole is a Pharmacist-Only Medicine, Appendix H listing will encourage more of our patients with heartburn to speak with the pharmacist about their condition. This is likely to have two positive health outcomes:

- Patients will receive the most appropriate OTC therapy for their condition.
- Patients with more severe disease or red flag symptoms will be referred to their GP earlier for clinical review.

With now more than 2 years in market experience of Pharmacist Only pantoprazole, I believe it is time to allow the public to be informed about this treatment option and support the listing of pantoprazole in Appendix H.

Declaration of interest. [redacted]

Yours sincerely,

[redacted]

[redacted]

[redacted]

14th January 2011

2.2.2 Pantoprazole - submission 10/10

The Secretary
Scheduling Secretariat
PO Box 9848,
Canberra ACT 2601, Australia

Dear Sir,

Re: Invitation for public comment: ACMS Meeting (23 February 2011) Agenda item 1.1 Pantoprazole – proposal to create a new entry for pantoprazole in Appendix H

In response to the invitation for public comment on the upcoming ACMS meeting (23 February 2011), [redacted] herewith provides the following submission in relation to the application for pantoprazole 20mg [redacted] to be included in Appendix H.

The application upon which the determinations are being based was submitted on 13 August 2010. Given that 5 months has transpired since that time, it is pertinent to provide an update on relevant data that has bearing under Section 52E of the *Therapeutics Goods Act 1989*.

Purpose and extent of use

[redacted] was first made available as a Schedule 3 medicine in October 2008. A comprehensive training program based on the principles of the quality use of medicines was developed and implemented at the time of the launch.

Research, undertaken after 12 months in-market use with this product, has demonstrated that Pharmacists are appropriately assessing and managing people presenting with frequent heartburn.[1] This research also demonstrates a high level of consumer label comprehension (a surrogate marker of appropriate use).

The Schedule 3 status of [redacted] dictates that Pharmacist intervention is required prior to the supply of the product. Branded advertising will inevitably drive demand for the product, due to increased awareness but it will not substantially change the manner in which patients would be assessed or managed in the Pharmacy setting. As such, there is no reason to believe that the purpose for which the substance is to be used would change in any way.

At the time of writing:

- [redacted] is the only PPI listed in Schedule 3 that has directly relevant in-market use data in the Australian setting.
- [redacted] is the only PPI listed in Schedule 3 that has published data demonstrating appropriate supply in the Australian setting.[1]
- Australian Pharmacists and consumers have more than 2 year's direct and relevant experience with the use of [redacted]

[redacted]

The toxicity of the substance

Our application provided information relating to the potential for an interaction between PPIs and clopidogrel. Subsequently, new data have been published (January 2011) that further confirm the position that this potential interaction is not a class effect.[2] This paper reports the results of four randomised, placebo-controlled, crossover studies. The authors conclude that the data support the presence of a true metabolic drug-drug interaction between clopidogrel and omperazole and that the interaction is not a class effect.

On the basis of the above data, it appears warranted that when making scheduling decisions the safety profiles of the individual active ingredients, rather than PPIs as a class, should be taken into consideration.

Public health benefit

The ability of Pharmacists to counsel customers and ensure that they leave the pharmacy setting with an appropriate product and/or advice is already established.[3]

[redacted] had previously put forward arguments to support the case that driving more heartburn sufferers into the pharmacy will positively impact public health by promoting a better use of this professional expertise; allowing discussion and assessment of frequent heartburn symptoms that would otherwise continue to be self-managed. This case is further supported by research demonstrating that when determining the suitability [redacted] Pharmacists are appropriately identifying customers with red flag symptoms and referring them to their GP for further investigation.[1]

[The Evaluation Report received in consideration of [redacted] September 2009 application for inclusion of the Schedule 3 pantoprazole 20 mg product in Appendix H agreed that the arguments presented were reasonable and that the data provided supported the proposed public health benefits.][1]

[redacted]

Concluding remarks

The primary purpose of direct-to-consumer advertising of Schedule 3 medicines, as articulated in the TGA report which guided the NCCTG's 1997 decision to allow such advertising, was the protection of public health and improvement in health outcomes. [redacted] submits that the ability to advertise [redacted] meets the primary purposes for which such advertising of it is intended.

---

[1] Commercial-in-Confidence

I trust that the above is of value. Should you require any further information, please do not hesitate to contact me on telephone [redacted]

Yours faithfully,

[redacted]

References

(1) Bell J, Katelaris P, Krassas G. *Aust Pharmacist* 2010;29(6):526-8.
(2) Angiolillo DJ, Gibson CM, Cheng S et al. *Clin Pharmacol Ther* 2011 January;89(1):65-74.
(3) Benrimoj C, et al. A Cost-Benefit Analysis of Pharmacist Only (S3) and Pharmacy Medicines (S2) and Risk-Based Evaluation of the Standards. 2005. Report No.: FINAL REPORT JUNE 2005.

[redacted]

Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

2.2.3 Rupatadine - submission 1/1

19 January 2011

Subject: **Public submission response to "Invitation for public comment…" re: Rupatadine** [redacted]

Dear Sir/Madam,

[redacted] provides the following response for consideration by the Advisory Committee for Medicines Scheduling (ACMS).

The Delegate's evaluation took into account, under subsection 52E(1) of the Therapeutic Goods Act 1989, the matter of part (b) *the purposes for which a substance is to be used....*; and subsequently requested advice from the scheduling committee regarding - Rupatadine shows some evidence of sedation which may warrant an Appendix K entry and a specific Schedule 4 entry for rupatadine would ensure clarity in interpretation.

EXECUTIVE SUMMARY

[redacted] believe that an Appendix K (App. K) entry is not warranted for Rupatadine [redacted] and have reviewed the Appendix F warning statements from the SUSMP No 1 which might apply if an App. K entry was made and provide the following assessment of those statements to assist the reviewer: - Statement 90, not applicable to the [redacted] product, as it is not a sleep aid product; - Statement 40, not applicable to the [redacted] product, as published clinical study data clearly demonstrate that rupatadine [redacted] combined with alcohol *did not* produce greater cognitive and psychomotor impairment compared with alcohol alone.[1] A comprehensive report by Jáuregui et al[2] published in 2006 also highlights little if any additive effect to alcohol induced impairment; - Statement 39, not applicable to the [redacted] product on the basis that published clinical study data with rupatadine [redacted] do not support a warning corresponding with not driving a vehicle or not operating machinery nor, as for statement 40 above, does clinical data support the statement to avoid alcohol. Therefore, in total, statement 39 should not be applied. [redacted] suggests that a specific Schedule 4 entry for rupatadine is not warranted as sedation in the case of [redacted] is not different to other second generation antihistamines. From clinical data it should be concluded that second generation antihistamines are *relatively* non-sedating compared with first generation antihistamines. [redacted] suggests that a non-sedating second generation antihistamine with zero somnolence does not currently exist and it should be entirely sufficient to include notification of potential for sedation in the Product Information documents.

Yours sincerely

[redacted]

1. SCHEDULING CONSIDERATION

In making the decision and on the basis of available information at the time, the Delegate noted 9 points, including the following:

- Rupatadine shows some evidence of sedation which may warrant an Appendix K entry.
- A specific Schedule 4 entry for rupatadine would ensure clarity in interpretation.

The Delegate (also) decided to refer a proposed Appendix K entry for advice from the Advisory Committee for Medicines Scheduling.

[redacted] understand the intent of an Appendix K entry is to provide a level of warning statement taken from Appendix F, Part 1, (statement 39, 40 or 90).

[redacted] provide the following assessment of those warning statements to assist the reviewer:

- Statement 90, not applicable to the [redacted] product as it is not a sleep aid product,

- Statement 40, not applicable to the [redacted] product as published clinical study data with rupatadine [redacted] combined with alcohol did not produce greater cognitive and psychomotor impairment compared with alcohol alone in a randomised, crossover, double-blind, placebo-controlled study of 18 healthy volunteers.[1]

- Statement 39, not applicable to the [redacted] product on the basis that published clinical study data with rupatadine [redacted] do not support a warning corresponding with not driving a vehicle or not operating machinery nor, as for statement 40 above, does clinical data support the statement to avoid alcohol. Therefore, in total, statement 39 should not be applied.

[redacted] suggests that a specific Schedule 4 entry for rupatadine is not warranted as sedation in the case of [redacted] is not different to other second generation antihistamines. From clinical data it should be concluded that second generation antihistamines are *relatively* non-sedating compared with first generation antihistamines. [redacted] suggests that a non-sedating second generation antihistamine with zero somnolence does not currently exist and, as somnolence is reported in a small minority of patients only, it should be entirely sufficient to include notification of potential for sedation in the Product Informatio cuments [redacted]

The non-significant effects of rupatadine on driving performance are also highlighted in a comprehensive report by Jáuregui et al[2] published in 2006,

[redacted]

Particularly in reference to sedation, [redacted] provided the following additional information [redacted]

Somnolence

The 2011 ICD-9-CM (International Classification of Diseases) Diagnosis code (780.09) for somnolence includes - a dulled or reduced level of alertness or consciousness; loss of ability to perceive and respond; or loss of ability to maintain awareness of self and environment combined with markedly reduced responsiveness to environmental stimuli.[3] It is well recognised that second generation antihistamines are generally non-sedating therapies, which avoid the somnolence and impaired psychomotor activity predominant with first generation anti-histamines.[5] Consistent with its selectivity for *peripheral* rather than CNS histamine H_1

receptors, rupatadine behaves similarly to second generation antihistamines and so is widely described in the published literature as "non-sedating". [11,13, 14] This does not mean that somnolence never occurs with these therapies.

[redacted] suggests that a non-sedating second generation antihistamine with zero somnolence does not currently exist and, as somnolence is reported in a small minority of patients, it should be concluded that second generation antihistamines are *relatively* non-sedating compared with first generation antihistamines. As with other non-sedating second generation antihistamines available in Australia for which somnolence is reported in < 10% of patients [6,7] (excluding cetirizine) somnolence occurred in 9.5% of rupatadine recipients from pooled clinical study data on 2025 patients as submitted in the [redacted]

Of further relevance is the lack of CNS effects such as cognitive and psychomotor impairment shown in both clinical and preclinical studies widely reported in the literature for the recommended therapeutic dose of rupatadine [redacted]. [5,11, 13-15]
Human studies in the [redacted] provide the following consistent evidence:

- Lack of psychomotor impairment activity for rupatadine [redacted] versus placebo, yet significant impairment for first generation antihistamine hydroxyzine 25 mg ($p=0.01$) and rupatadine [redacted] (both $p \leq 0.04$) which are [redacted] times the recommended therapeutic dose in a crossover randomised double-blind placebo-controlled study in 18 healthy volunteers[1]
- In a practical assessment of 'mental alertness' rupatadine [redacted] was not sedating and did not impair driving performance in a randomised, double-blind, three-way crossover placebo-controlled study of 20 healthy volunteers.[17] On various driving performance rupatadine [redacted] did not differ from placebo, whereas hydroxyzine 50mg was associated with impairment equivalent to that from a blood alcohol level of 0.9%[2].
  The non-significant effects of rupatadine on driving performance are also highlighted in a comprehensive on this matter by Jáuregui et al[2];
- Rupatadine [redacted] combined with alcohol did not produce greater cognitive and psychomotor impairment compared with alcohol alone in a randomised, crossover, double-blind, placebo-controlled study of 18 healthy volunteers.[1] Whereas alcohol with higher than the recommended rupatadine dose [redacted] and therapeutic doses of cetirizine (10 mg) and hydroxyzine (25mg) did produce greater cognitive and psychomotor decline than for alcohol alone, the greatest impairment occurred with hydroxyzine plus alcohol[1];

Repeated doses of rupatadine [redacted] in a crossover randomised double-blind placebo controlled trial of 16 healthy volunteers did not produce any significant changes in mental ability versus placebo.[18] Rupatadine [redacted] at steady state also did not enhance the CNS depressant effects of lorazepam 2 mg either in objective psychomotor tasks or in subjective evaluations of sedation.[18]

A tabulation of human studies which provide consistent evidence of absence of rupatadine-induced cognitive and psychomotor impairment is presented at Appendix 2 of this response.

[redacted]

Appendix 1 - References

1. Barbanoj MJ et al. Evaluation of the cognitive, psychomotor and pharmacokinetic profiles of rupatadine, hydroxyzine and cetirizine, in combination with alcohol, in healthy volunteers. Hum Psychopharmacol 2006;21(1):13-26
2. Jáuregui I et al. H1 antihistamines: psychomotor performance and driving. J Investig Allergol Clin Immunol 2006;16 (Suppl 1): 37-44
3. 2011 ICD-9-CM Diagnosis Code 780.09 Available at: http://www.icd9data.com/2011/Volume1/780-799/780-789/780/780.09.htm, Accessed 6 Jan '11
4. Maurer M et al. Unmet clinical needs in chronic spontaneous urticaria. A GA^{2}LEN task force report. Allergy 2010 [Epub ahead of print]
5. Mullol J et al. Rupatadine in allergic rhinitis and chronic urticaria. Allergy 2008;63(Suppl 87):5-28
6. Telfast and Tefodine Product Information, MIMs December 2010
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8. Jiménez-Arnau A et al. The use of responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20mg. JEADV 2009;23:1088-1091
9. Zuberbier et al. EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria. Allergy 2009;64:1427-1443
10. Valero A et al. Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis. Drug Safety 2009;32(1):33-42
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13. Picado C. Rupatadine: pharmacological profile and its use in the treatment of allergic disorders. Expert Opin Pharmacother 2006;7(14):1989-2001
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15. Keam SJ et al. Rupatadine. A review of its use in the management of allergic disorders. Drugs 2007;67(3):457-474
16. Barbanoj MJ et al. Central and peripheral evaluation of rupatadine, a new antihistamine/platelet-activating factor antagonist, at different doses in healthy volunteers. Neuropsychobiology 2004;50(4):311-321
17. Vuurman E et al. Lack of effects between rupatadine 10 mg and placebo on actual driving performance of healthy volunteers. Hum Psychopharmacol 2007;22(5):289-97.
18. García-Gea C, Rupatadine does not potentiate the CNS depressant effects of lorazepam: randomized, double-blind, crossover, repeated dose, placebo-controlled study. Br J Clin Pharmacol 2010;69(6):663-74
19. Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhinoconjunctivitis ; CHMP/EWP/2455/02.

Appendix 2

Tabulation of Human Studies Concerning Somnolence Related Findings.

Condition	**Rupatadine** 10mg, 20mg	**Hydroxyzine** 25 mg, 50 mg	**Cetririzine** 10 mg	**Rupatadine** 40 mg, * 80 mg * [redacted]	**Source**
Psychomotor impairment	None	Significant	N/A	Significant	Reference [1]
'Mental alertness in driving'	Not sedating. Did not impair driving performance	50 mg - impairment equivalent to that from a blood alcohol level of 0.9%[16].	N/A N/A		Reference [2]
Impairment from combining with alcohol	None (compared with alcohol alone)	Yes. 25 mg - significant impairment (compared with alcohol alone)	Yes. Significant impairment (compared with alcohol alone)	Yes. Significant impairment (compared with alcohol alone)	Reference [16]
Significant changes in mental ability	None	Not known	Not known	Not known	Reference [18]
Enhance the CNS depressant effects	No (combined with lorazepam 2 mg)	Not known	Not known	Not known	Reference [18]

END

2.2.5 Tapentadol - submission 1/4

[redacted]

14 January, 2011

Secretary
Scheduling Secretariat
Advisory Committee on Medicines Scheduling
Office of Chemical Safety and Environmental Health
Department of Health & Ageing
GPO Box 9848
CANBERRA ACT 2600

By facsimile: 6289 2500

Dear Sir/Madam,

Re: TAPENTADOL

It has been brought to my attention that the Advisory Committee is considering an Appendix D listing for tapentadol. As you are aware, this would restrict the prescription of tapentadol only to Pain Specialists.

This would have profound adverse ramifications for patients in their ability to access this medication in a timely and appropriate fashion, as the effective waiting list for most pain clinics is in excess of six months and in the face of dealing with complex chronic patients and then the additional burden of ticking the bureaucratic boxes for a General Practitioner to be able to prescribe tapentadol I can tell you what will happen. And that is that the patients will wait twelve months to be seen.

It is vitally important that General Practitioners are able to prescribe tapentadol in the same manner as they are currently able to prescribe tramadol, for which the current system works very well.

We know that the greatest risk for production of chronic pain is the inadequate treatment of acute pain and therefore if Appendix D listing occurs, the economic cost to society from inadequate treatment of pain and the subsequent increased burden of chronic pain is likely to be profound.

I urge the Committee to not apply an Appendix D listing to tapentadol. I am highly confident that the entire pain community would be shocked and distressed if this was to occur.

Yours sincerely,

[redacted]

2.2.5 Tapentadol - submission 2/4

[redacted]

17/01/2011 06:20 PM

To SMP@health.gov.au
cc
bcc
Subject Tapentadol proposal toinclude in Appendices D and K [SEC=No Protective

DOCUMENT NOT YET CLASSIFIED

14th January, 2011.

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA, ACT, 2601

I wish to make a public submission on Regulation 42ZCZK of the Therapeutic Goods Regulations 1990 in regard to the proposal to include Tapentadol in Appendices D and K.
I am an experienced rheumatologist, [redacted] I have a specific interest in chronic musculo-skeletal pain, having published widely in the areas of inflammatory joint disease, osteoarthritis, fibromyalgia and chronic pain in general.

Tapentadol has a unique mechanism of action, targeting both opioid and serotonin/noradrenaline reuptake pathways and clinical trials have shown significant outcomes in different conditions characterized by chronic pain.

There is a large burden of chronic pain in the Australian community much of which comes from chronic musculo-skeletal disease. Tapentadol will prove beneficial in management of these patients, most of whom are seen in primary care by general practitioners or on referral to rheumatologists and other clinicians. Many of these patients are old and face intractable pain with consequent disability and increased mortality. These patients already face long waiting times to gain access to specialist clinics.Restriction of prescribing would make this worse.
I am concerned that this medication may be unnecessarily restricted, through listing as Appendix D and K, to only selected craft groups and may not be available to the clinicians that look after all the health interests of the individual patients in a timely and efficient manner.

I understand that the listing to Appendix D and K is based on animal data in rabbits where very high doses were given, causing general ill health to the animals with some foetal abnormality. I further understand that the drug would be listed as Category C and would also be under Section 8. I think those latter restrictions would be enough to allow primary care and specialist clinicians to safely prescribe the medication.

There are a number of medications that are used that are Section 8 and Category C where appropriate patient selection is part and parcel of the pain management plan for any individual.

I note that rheumatologists, for instance, are used to dealing with medications that have Category C and potential foetal consequences, such as Leflunomide in younger women with rheumatoid arthritis.

Further, I am not aware that such restrictions have been placed on Tapentadol, or other drugs

which share the same mechanisms of action, in any other countries.
I think that the sole study indicating possible teratogenic potential would already be covered by the confirmed Schedule 8 listing of this drug.
It is important to weigh this potential risk against the benefits of better pain control for our community.
I believe that Tapentadol can be prescribed safely using standard restrictions applicable to this drug class.

[redacted]

[redacted]

2.2.5 Tapentadol - submission 3/4

The Secretary
Scheduling Secretariat
GPO Box 9498
Canberra ACT 2601

January 11th, 2011

Dear Secretary

RE: Public submission in reference to the proposal to include tapentadol in Appendix D

Please find enclosed a personal submission in relation to the above.

[redacted] I would like to draw light on the potential clinical implications of placing further restrictions – beyond those required by a necessary Schedule 8 listing – upon the prescription of tapentadol.

In the Australian clinical context, best practice pain management has long proved a challenging task. The formation of Faculty of Pain Medicine-accredited pain units has proved instrumental in improving outcomes for the many Australian patients experiencing pain, however the potential benefit of these centres is forever restricted by significantly long waiting lists. In South Australia, the time involved on such waiting lists is up to two years and beyond.

Through the formation of the National Network of Pain Management, an endorsed network of the RACGP National Faculty of Special Interests, [redacted] have identified the invaluable contribution of the primary care sector to evidence-based pain management. [redacted] and all those involved at Painaustralia's work is additional evidence of the importance of a multi-sectoral approach to pain management, and a Primary Care Working Group has been formed accordingly. This group is Chaired by [redacted] South Australian GP Dr Stephen Leow.

My primary concern with restricting tapentadol prescription to certain professional groups is that the burden on an already overwhelmed system will be exacerbated further. The current situation in the primary care sector evidences the unmet need for pain patients, and tapentadol is an additional management option of importance for this group. As such, it is imperative for tapentadol to be made appropriately accessible for pain patients in the primary care sector.

I trust that the above evidences the value of tapentadol in appropriately evaluated pain patients. This includes the primary care sector. If there is anything further I can provide, please feel free to let me know .

Yours sincerely

[redacted]

[redacted]

2.2.5 Tapentadol - submission 4/4

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Attention: The Secretary
Scheduling Secretariat

19 January 2011

Invitation for public comment – ACMS meeting regarding proposed amendments to the Poisons Standard

1.6 Tapentadol - proposal to include in Appendices D and K

Dear Sir/Madam,

Thank you for providing the opportunity to provide comment on the scheduling proposal for tapentadol, which will be considered at the 23 February 2011 meeting of the Advisory Committee on Medicines Scheduling (ACMS).

[redacted]

Should you have any questions or comments, please do not hesitate to contact the undersigned.

Yours sincerely

[redacted]

TAPENTADOL

Invitation for public comment – ACMS meeting regarding proposed amendments to the Poisons Standard

1.6 Tapentadol - proposal to include in Appendices D and K

Background

Effective pain management is fundamental to quality medical care of patients. Centrally acting analgesics, and in particular those with μ-opioid receptor agonist activity, have a long history of use in the treatment of moderate to severe pain and are widely used in the treatment of pain arising from chronic conditions. Discontinuation of treatment due to treatment related adverse events is a well known obstacle to successful pain treatment in clinical practice, especially for centrally acting analgesics.

Tapentadol is a new centrally acting opioid analgesic. It has a combined mode of action for its antinociceptive activity consisting of μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition. It thus shares pharmacological activities with pure μ-opioid analgesics (such as oxycodone and morphine) and with drugs with noradrenaline reuptake inhibitor activity (such as reboxetine and duloxetine).

Tapentadol has been approved in Australia by the Therapeutic Goods Administration (TGA) as an immediate release (IR) formulation for the relief of moderate to severe pain[1], and as a sustained release (SR) formulation for the management of moderate to severe chronic pain[2].

The results of the tapentadol clinical development program demonstrate a favourable safety profile for tapentadol. Importantly, tapentadol demonstrates an improved gastrointestinal tolerability profile compared with other strong opioids (such as oxycodone and morphine), resulting in a lower rate of treatment discontinuation due to adverse events. As noted in the TGA Australian Public Assessment Report (AusPAR) for tapentadol[3], this improved tolerability represents a clinically significant benefit and may translate to better patient compliance.

Tapentadol is also approved in many overseas countries, including the United States (US) where tapentadol has been available to patients since June 2009, and the European Union (EU).

Introduction

The Delegate has advised of her decision to list tapentadol in Schedule 8 of the Poisons Standard 2010, (in particular in Amendment No.1 to the Standard for the Uniform Scheduling of Medicines and Poisons 1), effective 1 January 2011. The Delegate has also noted that for entry into Appendix K and Appendix D, the advice of the Advisory Committee for Medicines Scheduling would be required.[4]

[redacted] contends that inclusion in Schedule 8 of the Poisons Standard (and an Appendix K listing) is an appropriate and sufficient control to ensure the safe and appropriate use of tapentadol in Australia. [redacted] however contends that an Appendix D listing for tapentadol is unwarranted and would be inappropriate.

[redacted] provides the enclosed comment on the Delegate's proposals.

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[1] The TGA approved indication for PALEXIA® IR is the relief of moderate to severe pain.

[2] The TGA approved indication for PALEXIA® SR is the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. There is currently no clinical trial data available regarding the safety and efficacy of PALEXIA® SR in patients with pain due to malignancy.

[3] Australian Public Assessment Report for tapentadol, PALEXIA® IR, December 2010. Unpublished as of the date of this Submission.

[4] Delegate´s reason for amendments to the Poisons Standard, December 2010, http://www.tga.gov.au/regulation/scheduling-decisions-1012.htm

a) Schedule 8

[redacted] agrees with the Delegate's decision to list tapentadol in Schedule 8 of the Poisons Standard. This is consistent with the classification of other μ-agonists approved in Australia, such as oxycodone, morphine, hydromorphone, fentanyl and other opioid analgesics. It is also consistent with equivalent scheduling of tapentadol in overseas countries such as the US (Schedule II of the Controlled Substances Act) and Germany ("Anlage III" of the German Law on Narcotic Drugs), and in all other countries in which the scheduling process has been completed.

The scheduling restrictions implied by these scheduling decisions overseas are equivalent to the Delegate's decision to include tapentadol in Schedule 8 of the Poisons Standard. Importantly, no additional controls have been recommended by any overseas Regulatory Authority.

b) Appendix K

[redacted] also agrees that it is appropriate to list tapentadol in Appendix K of the Poisons Standard. This is appropriate as tapentadol is associated with sedation effects (somnolence and lethargy), as is noted in the Precautions section of the TGA approved Product Information (PI). It is also consistent with other μ-agonists approved in Australia and overseas which are associated with sedation effects, such as oxycodone, morphine, hydromorphone, fentanyl and other opioids.

c) Appendix D

[redacted] contends that an Appendix D listing for tapentadol is unwarranted and would be inappropriate. In brief:

i) An Appendix D listing would be inappropriate because it would unnecessarily restrict the availability of tapentadol by limiting tapentadol prescription to particular specialities.

ii) The Delegate comments that "*tapentadol is classified by the US Food and Drug Administration (FDA) as a Category C pregnancy drug (drugs which should be given only if the potential benefit justifies the potential risk to the foetus)".* The Delegate further states that "*Pre-clinical studies have revealed teratogenic effects in animals; however no controlled teratogenicity studies in humans have been reported. These effects may warrant an Appendix D entry*"[5].

[redacted] believes that this conclusion cannot be derived from the pregnancy C classification by the US FDA and is not an accurate reflection of the data available from teratogenicity studies of tapentadol. Furthermore, [redacted] contends that the results of these studies support the conclusion that tapentadol is <u>not</u> teratogenic in animals. Of note, the EU SmPC explicitly notes that "*studies in animals have not shown teratogenic effects."*

[5] Delegate´s reason for amendments to the Poisons Standard, December 2010, http://www.tga.gov.au/regulation/scheduling-decisions-1012.htm

iii) [redacted] contends that the advice on the use of tapentadol in pregnancy provided in the TGA approved Australian PI, together with its Category C classification, is appropriate and adequate to assist clinicians to make appropriate prescribing decisions and to prevent a broad, uncontrolled use of tapentadol in pregnant women. This advice is the same as that approved by the US and EU Regulatory Authorities for tapentadol (in the US PI and EU SmPC, respectively). It is also the same advice as that approved for drugs with a similar mode of action. Importantly, none of these drugs are included in Appendix D (or equivalent) in either Australia or overseas.

iv) Data from clinical trials and overseas post-marketing experience with tapentadol support the view that tapentadol is being prescribed appropriately and that additional controls (beyond Schedule 8) are unnecessary.

The above reasons for why an Appendix D listing is considered inappropriate for tapentadol are elaborated on below.

1. Clinical place of tapentadol in pain management

An Appendix D listing for tapentadol would be inappropriate because it would unnecessarily restrict the availability of tapentadol by limiting its prescription to particular specialities.

In Australian clinical practice, moderate to severe pain is managed both at a specialist and primary care level, and the trend in best practice of these patients is a shared care, multi-faceted approach to their pain with multiple health care professionals involved. The current waiting times for a pain specialist maybe up to 2 years in some areas. Additionally, in the National Pain Strategy (developed by the Australian National Pain Summit Initiative) it is advised to integrate the primary care sector with interdisciplinary pain clinics in the tertiary sector as "with only 269 Fellows of the Faculty, pain specialists are unable to service 20 per cent of the population" [6]. The recommendation here is to empower primary care with the knowledge to utilise treatment options appropriately. These circumstances highlight the importance of having tapentadol available to general practitioners to prescribe for the appropriate patients. It would be impractical and unreasonable to expect patients suffering from moderate to severe pain to wait unnecessarily for treatment for up to potentially 2 years. Doing so may further exacerbate their illness and impact negatively on their quality of life.

As patients seeking pain relief from moderate to severe pain seek help from both general practitioners and a wide variety of medical specialists, [redacted] believes it would be difficult to accurately identify all classes of clinicians who would likely prescribe the drug.

[6] *National Pain Strategy - Pain Management for all Australians*, Developed by the National Pain Summit initiative in March 2010, www.painsummit.org.au

2. Summary of the preclinical data

a) Preclinical data assessed by the TGA and overseas Regulatory Authorities

[redacted] contends that the results of the tapentadol preclinical studies support the conclusion that tapentadol is not teratogenic in animals.

In accordance with international guidelines on risk assessment of medicinal products[7], preclinical data on the potential teratogenic effects of tapentadol have been conducted in embryo-foetal development studies in rats and rabbits using both the intravenous and subcutaneous route of administration. The reports of these studies are part of the global registration dossier of tapentadol and as such were evaluated by the Australian TGA, US Food and Drug Administration (FDA), and European Medicines Agency (EMA).

[redacted]

[redacted]

[redacted]

[redacted]

b) Summary of preclinical data in the TGA approved PI and overseas approved PI documents

[redacted] conclusion that tapentadol is not teratogenic in animals is shared by overseas Regulatory Authorities that have approved tapentadol, as evidenced by the respective Product Information (PI) texts.

The TGA approved Australian PI (see "Precautions – Use in Pregnancy (Category C)) reads as follows:

"Tapentadol was evaluated for teratogenic effects in rats and rabbits following intravenous and subcutaneous administration during organogenesis. Embryofetal toxicity such as delays in skeletal maturation and cerebral ventricular dilation was observed in rats concomitant with maternal toxicity at subcutaneous doses of 10 mg/kg/day or greater (plasma AUC exposure less than maximum anticipated clinical exposure). Subcutaneous administration of tapentadol to rabbits revealed embryofetal toxicity at doses of 10-24 mg/kg/day (AUC exposure 1 to 2 fold the maximum anticipated human exposure), along with reduced fetal viability, skeletal delays and other variations, and multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia and cleft palate at 10-24 mg/kg/day, and ablepharia, encephalopathy and spina bifida at 24 mg/kg/day. There were no teratogenic effects observed in similar studies conducted in rats and rabbits via the intravenous route (up to 15 mg/kg/day). Embryofetal toxicity, including malformations, may be secondary to maternal toxicity in these species."

The above TGA approved precautionary information regarding the use of tapentadol in pregnant women is very similar, albeit more detailed, to the respective information in the approved US PI [redacted] (Appendix 1[redacted]).

[redacted]

Importantly, the preclinical data set upon which all texts quoted above are based is identical to the data that was evaluated in Australia by the TGA.

The regulatory controls in place in the US and the EU clearly indicate that use of tapentadol can be adequately controlled via its Controlled Substance (Schedule 8 equivalent) scheduling status and the Precautions described in the approved Product Information.

Hence, [redacted] firmly believes that there is no justification for additional controls in Australia.

3. Advice on use of tapentadol in pregnancy, and other approved drugs with a similar mode of action

The TGA approved PI for tapentadol provides adequate advice to the clinician about use during pregnancy.

Tapentadol exhibits μ-opioid receptor agonism and noradrenaline reuptake inhibition, thus sharing pharmacological activities with pure μ-opioid analgesics and with drugs with noradrenaline reuptake inhibitor activity. The classification of tapentadol as a Pregnancy Category C drug is appropriate and is consistent with the similar classification of other μ-opioid analgesics and drugs with noradrenaline reuptake inhibitor activity in Australia. Moreover, the approved PIs of all of these drugs clearly state that such drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Importantly, other pure μ-opioid analgesics do not include any additional controls on possession or supply beyond Schedule 4 or Schedule 8, and Appendix K (for opioids only). Hence, an Appendix D listing would be inconsistent with the scheduling decisions in place for drugs with a similar mechanism of action and could potentially result in prescriber confusion and subsequent suboptimal treatment of patient pain.

4. Clinical experience

Data from clinical trials and overseas post-marketing experience with tapentadol support the view that tapentadol is being prescribed appropriately and that additional controls (beyond Schedule 8) are unnecessary.

[redacted] Data from human clinical trials and post-marketing experience with tapentadol do not suggest any evidence for teratogenicity.

For ethical reasons, no controlled teratogenicity trials have been conducted in humans. Therefore, experience of the effects of tapentadol administration during pregnancy is limited to pregnancies incidentally occurring during the clinical trial program or post-marketing. [redacted]

[redacted] is thus of the opinion that the advice included in the TGA approved Product Information regarding the use of tapentadol in pregnancy (that is, tapentadol "*should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus")* together with its classification as a Schedule 8 and Category C drug is adequate to prevent a broad, uncontrolled use of tapentadol in pregnant women, just as it is for the respectively classified pure μ-opioid agonists or noradrenaline reuptake inhibitors.

Conclusion

In conclusion, [redacted] agrees with the Delegate's decision to list tapentadol in Schedule 8, and agrees that it is appropriate to include tapentadol in Appendix K of the Poisons Standard. This is consistent with the scheduling decisions made for other opioids approved in Australia and overseas.

However, [redacted] contends that tapentadol should not be included in Appendix D of the Poisons Standard. An Appendix D listing is considered inappropriate because:

- The availability of tapentadol would be restricted beyond the controls in place for all other μ-opioids approved in Australia for the treatment of moderate to severe pain. This would unnecessarily restrict the availability of tapentadol by limiting tapentadol prescription to particular specialities and could potentially result in negative patient outcomes (see Section 1 of this submission). Tapentadol, given its overall benefit risk profile, and in particular its improved gastrointestinal tolerability profile, represents a useful addition to the treatment options for pain patients. It should therefore be available to all prescribers to the same extent as other μ-opioids in Australia.
- Studies in animals have not shown teratogenic effects
- The TGA approved Product Information for the use of tapentadol during pregnancy is appropriate and adequate to assist clinicians to make appropriate prescribing decisions and to prevent a broad, uncontrolled use of tapentadol in pregnant women. The approved prescribing information of tapentadol both in Australia and overseas, clearly states that such drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
- Data from clinical trials and overseas post-marketing experience with tapentadol support the view that tapentadol is being prescribed appropriately and that additional controls (beyond Schedule 8) are unnecessary.

Therefore, [redacted] contends that inclusion in Schedule 8 of the Poisons Standard (and an Appendix K listing) is an appropriate and sufficient control to ensure the safe and appropriate use of tapentadol in Australia.

References

[redacted]

National Pain Strategy - Pain Management for all Australians, Developed by the National Pain Summit initiative in March 2010, www.painsummit.org.au

[redacted]

Appendix 1

Excerpt from Approved US PI. The relevant text is highlighted.

Gastrointestinal disorders: abdominal discomfort, impaired gastric emptying

General disorders and administration site conditions: irritability, edema, drug withdrawal syndrome, feeling drunk

Immune system disorders: hypersensitivity

Investigations: gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased

Musculoskeletal and connective tissue disorders: involuntary muscle contractions, sensation of heaviness

Nervous system disorders: hypoesthesia, paresthesia, disturbance in attention, sedation, dysarthria, depressed level of consciousness, memory impairment, ataxia, presyncope, syncope, coordination abnormal, seizure

Psychiatric disorders: euphoric mood, disorientation, restlessness, agitation, nervousness, thinking abnormal

Renal and urinary disorders: urinary hesitation, pollakiuria

Respiratory, thoracic and mediastinal disorders: oxygen saturation decreased, cough, dyspnea, respiratory depression

Skin and subcutaneous tissue disorders: urticaria

Vascular disorders: blood pressure decreased

In the pooled safety data, the overall incidence of adverse reactions increased with increased dose of NUCYNTA®, as did the percentage of patients with adverse reactions of nausea, dizziness, vomiting, somnolence, and pruritus.

6.3 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of NUCYNTA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably.

Nervous system disorders: headache

Psychiatric disorders: hallucination

7 DRUG INTERACTIONS

NUCYNTA® is mainly metabolized by glucuronidation. The following substances have been included in a set of interaction studies without any clinically significant finding: acetaminophen, acetylsalicylic acid, naproxen and probenecid *[see Clinical Pharmacology (12.3)]*.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively *[see Clinical Pharmacology (12.3)]*.

7.1 Drugs Metabolized by Cytochrome P450 Enzymes

In vitro investigations indicate that NUCYNTA® does not inhibit or induce P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs That Inhibit or Induce Cytochrome P450 Enzymes

The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. To a lesser extent, tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Since only a minor amount of NUCYNTA® is metabolized via the oxidative pathway clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3)]*.

7.3 Centrally-Acting Drugs and Alcohol

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered *[see Warnings and Precautions (5.2) and (5.6)]*.

7.4 Monoamine Oxidase Inhibitors

NUCYNTA® is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events *[see Contraindications (4.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Tapentadol HCl was evaluated for teratogenic effects in pregnant rats and rabbits following intravenous and subcutaneous exposure during the period of embryofetal organogenesis. When tapentadol was administered twice daily by the subcutaneous route in rats at dose levels of 10, 20, or 40 mg/kg/day [producing up to 1 times the plasma exposure at the maximum recommended human dose (MRHD) of 700 mg/day based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofetal toxicity included transient delays in skeletal maturation (i.e. reduced ossification) at the 40 mg/kg/day dose which was associated with significant maternal toxicity. Administration of tapentadol HCl in rabbits at doses of 4, 10, or 24 mg/kg/day by subcutaneous injection [producing 0.2, 0.6, and 1.85 times the plasma exposure at the MRHD based on an AUC comparison] revealed embryofetal toxicity at doses ≥ 10 mg/kg/day. Findings included reduced fetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses ≥ 10 mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

In a study of pre- and postnatal development in rats, oral administration of tapentadol at doses of 20, 50, 150, or 300 mg/kg/day to pregnant and lactating rats during the late gestation and early postnatal period [resulting in up to 1.7 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses ≥ 150 mg/kg/day, a dose-related increase in pup mortality was observed through postnatal Day 4.

There are no adequate and well controlled studies of NUCYNTA® in pregnant women. NUCYNTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of tapentadol on labor and delivery in humans is unknown. NUCYNTA® is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of NUCYNTA®, neonates whose mothers have been taking NUCYNTA® should be monitored for respiratory depression. A specific opioid antagonist, such as naloxone, should be available for reversal of opioid induced respiratory depression in the neonate.

8.3 Nursing Mothers

There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. NUCYNTA® should not be used during breast-feeding.

8.4 Pediatric Use

The safety and effectiveness of NUCYNTA® in pediatric patients less than 18 years of age have not been established. NUCYNTA® is not recommended in this population.

8.5 Geriatric Use

Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of NUCYNTA®, 19% were 65 and over, while 5% were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. The rate of constipation was higher in subjects greater than or equal to 65 years than those less than 65 years (12% vs. 7%).

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

In patients with severe renal impairment, the safety and effectiveness of NUCYNTA® has not been established. NUCYNTA® is not recommended in this population *[see Dosage and Administration (2.1)]*.

8.7 Hepatic Impairment

Administration of NUCYNTA® resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. NUCYNTA® should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.2)]*.

NUCYNTA® has not been studied in patients with severe hepatic impairment, therefore, use of NUCYNTA® is not recommended in this population *[see Warnings and Precautions (5.10)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

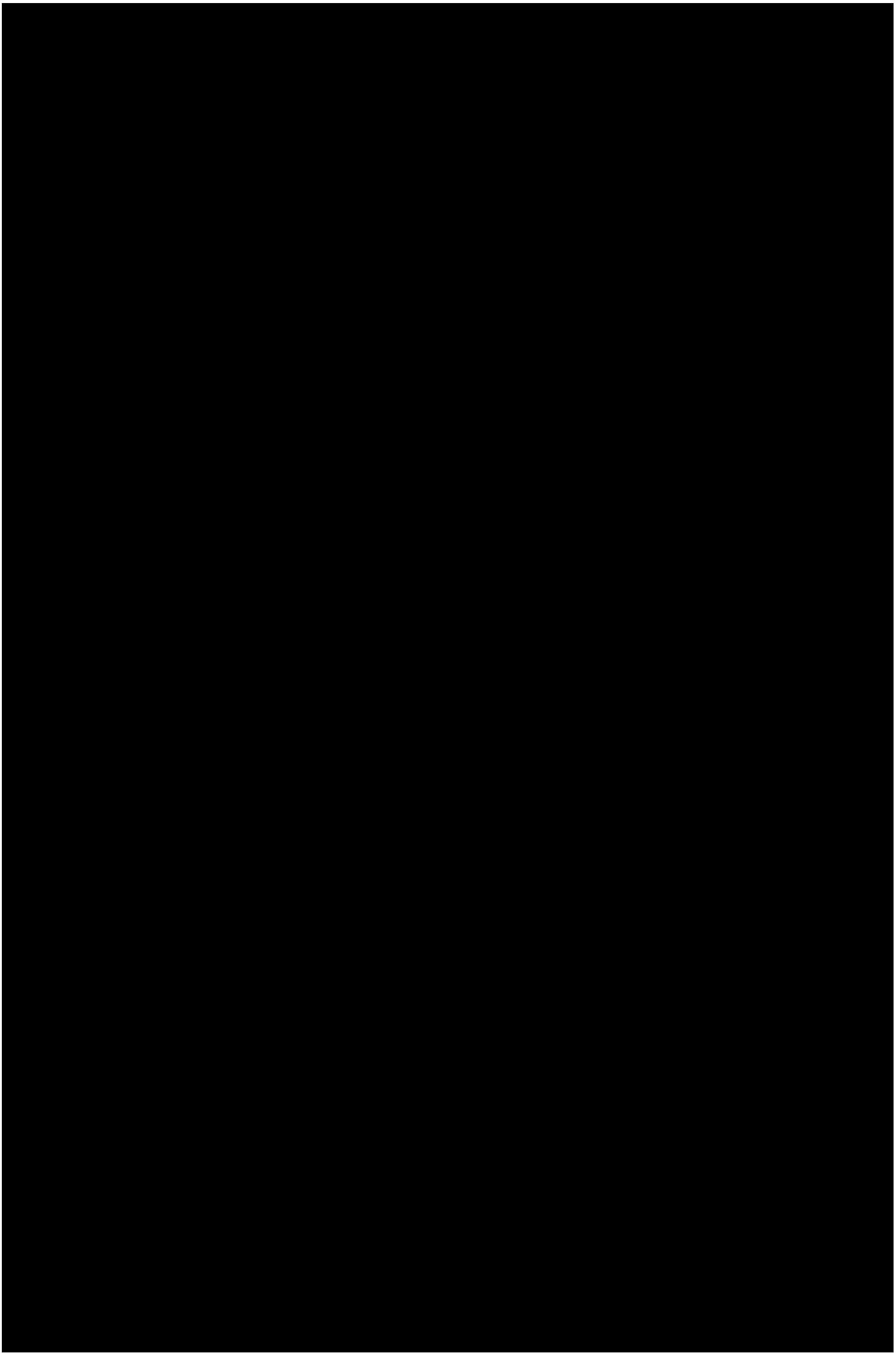
NUCYNTA® contains tapentadol, a mu-opioid agonist and is a Schedule II controlled substance. NUCYNTA® has an abuse potential similar to hydromorphone, can be abused and is subject to criminal diversion.

9.2 Abuse

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

[redacted]

[redacted]



[redacted]

SUBMISSION FOR THE FEBRUARY 2011 MEETING OF THE ADVISORY COMMITTEE ON MEDICINES SCHEDULING

2.3 Multiple submission 1/1

PURPOSE

1. [redacted] makes this submission in relation to items referred by the Delegate (on 15 and 16 December 2010) to the Advisory Committee on Medicines Scheduling (ACMS) for scheduling advice.

2. Comments are provided on chloramphenicol, paracetamol + ibuprofen combination, pantoprazole, ibuprofen and fexofenadine.

RECOMMENDATIONS

3. [redacted] provides the following recommendations to the ACMS:

   a. **Chloramphenicol.** [redacted] does not object to the proposal to restrict use in Schedule 3 to the treatment of bacterial conjunctivitis.

   b. **Paracetamol + ibuprofen combination.** [redacted] believes the appropriate schedule for paracetamol and ibuprofen combination products is Schedule 2 for smaller pack sizes and Schedule 3 for larger pack sizes.

   c. **Pantoprazole.** [redacted] supports the proposal for inclusion in Appendix H.

   d. **Ibuprofen.** [redacted] does not object to the proposal to increase the Schedule 2 limit on liquid preparations but believes it should not exceed 8 g.

   e. **Fexofenadine.** [redacted] believes the current Schedule 2 entry for fexofenadine remains appropriate and is firmly opposed to any proposal to exempt from scheduling requirements.

CHLORAMPHENICOL

4. [redacted] does not object to the proposal to amend the Schedule 3 entry for chloramphenicol to restrict use to the treatment of bacterial conjunctivitis. The document issued by PSA in May 2010, *Provision of chloramphenicol for ophthalmic use as a Pharmacist Only medicine*, provides guidance to pharmacists on the appropriate use of chloramphenicol in bacterial conjunctivitis, including how to differentiate it from viral conjunctivitis and allergic conjunctivitis.

PARACETAMOL + IBUPROFEN COMBINATION

5. The scheduling of paracetamol and ibuprofen combination products has been considered recently and as more detail for this agenda item is not available, it is somewhat difficult to provide comment.

6. In a previous submission, [redacted] noted a study[1] which showed that a combination of paracetamol 500 mg and ibuprofen 150 mg provided superior pain relief (after oral surgery) to paracetamol or ibuprofen alone. [redacted] also noted the inherent safety profile of each

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[1] Merry AF, Gibbs RD, Edwards J, Ting GS, Frampton C, Davies E, Anderson BJ. Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. Br J Anaesth 2010; 104(1): 80–8.

substance is well established. However, a combination product carries a wider spectrum of precautions and potential side effects or interactions.

7. The current Schedule 2 entry allows a maximum pack size of 100 dosage units of a combination product. [redacted] believes this is excessive considering the product's recommended maximum of six dosage units per day and three days' supply. In addition, there are many other products available over-the-counter with one of these active ingredients. This presents many more opportunities for duplication of the ingredients sourced through multiple products.

8. [redacted] believes it is appropriate to have smaller pack sizes of paracetamol and ibuprofen combination products in Schedule 2 while larger packs (eg. a maximum pack size of 100 dosage units) should be in Schedule 3.

PANTOPRAZOLE

9. [redacted] notes a proposal to include pantoprazole in Appendix H has been considered previously.

10. As noted in [redacted] previous submissions, a sponsor of pantoprazole 20 mg has been fulfilling the commitment it made prior to the rescheduling to Schedule 3 to work with pharmacy stakeholders in an ongoing manner. This has included the delivery of education, training and resources to pharmacists nationally, and consultation regarding consumer-based research. This is consistent with [redacted] view that sponsors should invest in appropriate education for the profession (including non-pharmacist staff), and where appropriate, consumers.

11. In the community pharmacy setting, non-pharmacist staff members have an important role in assisting with the supply of therapeutic goods and referring the consumer to a pharmacist when required for certain products and conditions. There is scope for more comprehensive education to be delivered to this sector of the pharmacy workforce. [redacted] believes Appendix H listing for pantoprazole will appropriately enable further investment in education events and resources for non-pharmacist pharmacy staff.

12. Appendix H listing would also allow advertising to consumers. Advertising to the public already occurs for several Schedule 2 and unscheduled products which are used to treat uncomplicated gastro-oesophageal reflux disease. The inclusion of pantoprazole in Appendix H would therefore better align the information made available to consumers regarding this category of products. This would assist consumers in making an informed choice.

13. [redacted] supports the proposal to include pantoprazole in Appendix H.

IBUPROFEN

14. [redacted] notes this proposal has the potential to permit more concentrated liquid preparations (eg. a „double strength' preparation for children if an 8 g upper limit is agreed) and/or larger pack sizes.

15. In principle, [redacted] does not object to this proposal. However, we note the scheduling meeting notice states the proposal is to increase the limit to "at least" 8 g or less. In the absence of further information, it is not possible to understand the rationale for this wording. [redacted] believes the upper limit must not exceed 8 g.

FEXOFENADINE

16. Seasonal allergic rhinitis is a common presentation in community pharmacy and there are many products available to effectively manage these symptoms. The condition can usually be recognised by consumers and is suitable for short-term, self-treatment.

17. There are, however, circumstances which necessitate professional intervention and some instances when this would be vital, for example:

a. to provide information and counselling at the time of supply of a product;

b. when other causes (eg. an infection or more acute illness) may be suspected;

c. for advice on follow-up when original symptoms have not resolved after a few days;

d. when the person has reported reliance (ie. more than intermittent use) on a medication intended for short-term treatment; and/or

e. when referral to a medical practitioner is warranted.

18. The current Schedule 2 entry allows fexofenadine in preparations for oral use to be made available to consumers from an environment where professional advice and intervention can be provided, at the time of purchase of the product, or during a period of follow-up and monitoring. [redacted] believes this is vital from a patient safety perspective and to ensure optimal use of such medicines. Such safeguards will not be available to consumers if the substance is exempted from scheduling regardless of any warning statements included through product packaging and labelling.

19. [redacted] notes the various conditions or criteria (eg. pack size, maximum daily dose) which have been suggested as part of this proposal to exempt fexofenadine from scheduling requirements. However, [redacted] is firmly opposed to any proposal to exempt fexofenadine from scheduling.

Submitted by:

[redacted]

Contacts:

[redacted]

[redacted]

19 January 2011

[redacted]

19th January 2011 **3.1 Methylsulfonylmethane / dimethyl sulfone - submission 1/3**

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Re: Joint meeting of the Advisory Committees on Medicines and Chemicals Scheduling (ACMS and ACCS) 28th Feb. 2011-01-18

Agenda Item 3.1
Methylsulfonylmethane - consideration of inclusion of methylsulfonylmethane (MSM) in Schedule 4 for human therapeutic use in concentrations greater than 1500 mg per dosage unit. This consideration may also include methylsulfonylmethane for non-human use, mirroring the scheduling of dimethyl sulfoxide.

[redacted] appreciates the opportunity to provide comment in relation to this issue. We wish to address relevant matters under section 52E of the Therapeutic Goods Act 1989 as these apply to the substance mentioned above: (a) risks; and (b) toxicity.

[redacted] is **not** in favour of the proposal to schedule Dimethyl sulfone (Methylslfonylmethane).

Firstly, there appears to be no valid safety concern to justify restricting this substance.

- Normal usage ranges from 1.5 to 10g daily, commonly in divided doses.
- Rat studies employing doses up to 8g per kg bodyweight per day revealed no toxic effects.
- Rat developmental studies have established a NOAEL of 1000mg/kg/day.
- Mutagenicity studies have shown negative results.
- A human study utilising 2600mg per day demonstrated few side effects.
- We are unaware of the existence of any safety signal in Australia concerning Dimethyl sulfone.

Secondly, the TGA has previously evaluated this substance for use in listed medicines.

- It was accepted as suitable for use in listed medicines, meaning that it was judged to be safe for use without supervision.
- The listing notice contains no restriction on dose.
- The same notice contains no requirement for a warning label for this substance.

Thirdly, while there have been some concerns over Dimethyl sulfoxide:

- Although the two substances are chemically related, Dimethyl sulfone is not the same entity.
- Dimethyl sulfone is used and recommended in preference to Dimethyl sulfoxide because of its greater safety.

In summary, we are concerned that scheduling is being considered in the absence of clear need, and apparently without reasonable scientific justification. We consider such an action inappropriate and unnecessary.

We note also that the committee refers to this substance as Methylsulfonylmethane. We request that the AAN, Dimethyl sulfone, be used.

[redacted]

For your reference, please find attached copies of:

- The Swedish Medical Library (EBSCO) monograph
- The Alternative Medicine Review monograph
- The TOXNET reference on developmental toxicology in rats
- The TOXNET reference on mutagenicity
- The abstract of the human study utilising 2600mg/day
- The abstract of the study in mice using up to 8g/kg/day.

Sincerely yours,

SWEDISH

Patient & Visitor Information
Health Library

Methyl Sulfonyl Methane (MSM)

Supplement Forms/Alternate Names
MSM

Related Terms
Dimethyl Sulfone ($DMSO_2$)

Principal Proposed Uses
Osteoarthritis

Other Proposed Uses
Improving Growth of Nails and Hair; Interstitial Cystitis; Rheumatoid Arthritis; Rosacea; Snoring; Sports Injuries

MSM (methyl sulfonyl methane) is a sulfur-containing compound normally found in many of the foods we eat. It is chemically related to DMSO (dimethyl sulfoxide), a popular (although unproven) treatment for arthritis. When DMSO is applied on the skin or taken orally, about 15% of it breaks down in the body to form MSM.[1]

Some researchers have suggested that the resulting MSM could be responsible for the benefits attributed to DMSO. If so, MSM might be preferable as a treatment, because it does not cause some of the unpleasant side effects associated with DMSO treatment, such as body odor and bad breath. In addition, as a natural substance found in food, MSM would be expected to have a good safety profile. However, there is as yet no more than preliminary evidence that MSM is useful for any medical condition.

Requirements/Sources

There is no dietary requirement for MSM. However, it occurs naturally in cow's milk, meat, seafood, vegetables, fruits, and even coffee, tea, and chocolate. MSM supplements are sold in healthfood stores and some pharmacies. Although creams and lotions containing MSM are also available, it is hard to see the purpose of these topical products since MSM, unlike DMSO, is not absorbed through the skin.[2]

MSM supplies sulfur. Some advertisements for MSM claim that sulfur deficiency is widespread, and that for this reason alone MSM will improve the health of most everybody who takes it. However, there are numerous other dietary sources of sulfur, including, most prominently, many forms of ordinary protein.

Therapeutic Dosages

Dosages of oral MSM used for therapeutic purposes range from 1,500 to 10,000 mg daily, usually divided up into 3 daily doses.

Therapeutic Uses TOP

Two small double-blind, placebo-controlled studies indicate that MSM may be helpful for osteoarthritis.[16,17]

In one small, placebo-controlled trial, the topical application of methylsulfonylmethane with silymarin (milk thistle) for 1 month appeared to be effective in the treatment of 46 subjects with the skin condition rosacea.[19]

Small, unpublished trials have been used to claim that MSM is effective for the treatment of snoring, aiding the growth of nails and hair, and assisting in recovery from sports injuries.[7,13-14] However, the design of each of these studies was substandard, and the results were not subjected to any proper statistical analysis; therefore, they cannot be taken as meaningful evidence of efficacy.

One study in mice found positive effects of MSM in the treatment of rheumatoid arthritis.[4] Other animal studies hint that MSM might have cancer preventive properties.[8,9,10] Human studies on these potential uses of MSM have not been reported.

MSM has also been proposed as a treatment for interstitial cystitis, an inflammation in the wall of the bladder that causes frequent and painful urination. When prescribed for this condition, MSM is usually instilled directly into the bladder, although oral use has also been suggested. However, no clinical studies on this use have been performed: the only evidence for this treatment comes from case studies and anecdotal reports.[5] Since interstitial cystitis is known to respond very positively to placebo,[6] these reports mean little.

MSM has also been advocated for allergies (including drug allergies), scleroderma, excess stomach acid, and constipation, but there is no meaningful evidence whatsoever to support these proposed uses.

What Is the Scientific Evidence for Methyl Sulfonyl Methane? TOP

In a double-blind, placebo-controlled study performed in India, 118 people with osteoarthritis of the knee were given one of the following four treatments: glucosamine (500 mg, 3 times daily), MSM (500 mg, 3 times daily), a combination of glucosamine and MSM, or placebo.[16] The study ran for 12 weeks. The results showed that both MSM and glucosamine improved arthritis symptoms as compared to placebo, and that the combination of MSM and glucosamine was more effective than either one alone. Benefits were also seen in a 12-week, double-blind, placebo-controlled trial of 50 people with osteoarthritis, utilizing MSM at a dose of 3 g twice daily.[18]

However, in a comprehensive review of 6 studies involving 681 patients with osteoarthritis of knee, researchers

concluded it is not yet possible to convincingly determine whether or not either DMSO or MSM is beneficial.[20]

Safety Issues TOP

MSM is a natural component of the foods we normally eat and is not believed to be toxic. A laboratory study examining doses up to 8 g per kilogram of body weight per day (about 250 times the highest dose normally used by humans) reported that no toxic effects were seen.[12]

Maximum safe doses for young children, pregnant or nursing women, or people with liver or kidney disease are not known. Possible drug interactions are also not known.

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Last reviewed August 2010 by EBSCO CAM Review Board
Last Updated: 8/1/2010

J Altern Complement Med. 2002 Apr;8(2):167-73.

A multicentered, open-label trial on the safety and efficacy of methylsulfonylmethane in the treatment of seasonal allergic rhinitis.

Barrager E, Veltmann JR Jr, Schauss AG, Schiller RN.

GENESIS Center for Integrative Medicine, Graham, WA, USA.

Comment in:

J Altern Complement Med. 2002 Jun;8(3):229.

Abstract

BACKGROUND: Seasonal allergic rhinitis (SAR) affects more than 23 million Americans annually, and current epidemiologic studies indicate that its prevalence within the United States is increasing. Numerous clinical observations and case studies have led researchers to hypothesize that methylsulfonylmethane (MSM) may help ameliorate the symptoms associated with SAR.

OBJECTIVE: The primary goal of this study was to evaluate the efficacy of MSM in the reduction of SAR-associated symptoms. This study also examined possible adverse reactions associated with methylsulfonylmethane supplementation. Finally, this study attempted to elucidate the method of action by which MSM elicits its effect on allergy symptoms.

DESIGN: Fifty-five (55) subjects were recruited for the study. All met the criteria for participation in the study. 50 subjects completed the study. Those subjects completing the study consumed 2,600 mg of MSM orally per day for 30 days. Clinical respiratory symptoms and energy levels were evaluated by a Seasonal Allergy Symptom Questionnaire (SASQ) at baseline and on days 7, 14, 21, and 30. Immune and inflammatory reactions were measured by plasma immunoglobulin E (IgE) and C-reactive protein at baseline and on day 30. An additional inflammatory biomarker, plasma histamine, was measured in a subset of subjects (n = 5).

RESULTS: Day 7 upper and total respiratory symptoms were reduced significantly from baseline ($p < 0.01$ and $p < 0.005$, respectively). Lower respiratory symptoms were significantly improved from baseline by week 3 ($p < 0.001$). All respiratory improvements were maintained through the 30-day visit. Energy levels increased significantly by day 14 ($p < 0.0001$); this increase continued through day 30. No significant changes were observed in plasma IgE or histamine levels. The results of this study are promising. It would be worthwhile to conduct a larger, randomized, double-blind, placebo-controlled study to establish further if MSM would be a useful agent in the treatment of symptoms associated with SAR.

CONCLUSION: The results of this study suggest that MSM supplementation of 2,600 mg/day for 30 days may be efficacious in the reduction of symptoms associated with SAR. Furthermore, few side effects are associated with the use of this compound. Recent acute and subacute chronic toxicologic data on the same source of MSM as used in this study, further validate the safety of this product.

PMID: 12006124 [PubMed - indexed for MEDLINE]

Proc Soc Exp Biol Med. 1986 Nov;183(2):227-30.

Effects of oral dimethyl sulfoxide and dimethyl sulfone on murine autoimmune lymphoproliferative disease.

Morton JI, Siegel BV.

Abstract

The results from several studies examining the effects of DMSO on autoimmune phenomena have been inconclusive, possibly because of differences in experimental models, treatment regimens and doses employed. In the present investigation, autoimmune strain MRL/lpr, C3H/lpr, and male BXSB mice were placed on a continuous treatment regimen with 3% DMSO or 3% DMSO2 in the drinking water, ad libitum, commencing at 1 to 2 months of age, before spontaneous disease development could be detected. This represented doses of 8-10 g/kg/day of DMSO and 6-8 g/kg/day of DMSO2. Both compounds were observed to extend the mean life span of MRL/lpr mice from 5 1/2 months to over 10 months of age. All strains showed decreased antinuclear antibody responses and significant diminution of lymphadenopathy, splenomegaly, and anemia development. Serum IgG levels and spleen IgM antibody plaque formation, however, did not differ from control values. There was no indication of involvement of systemic immunosuppressive or antiproliferative effects, and treated animals were observed to remain healthy and vigorous with no signs of toxicity. These results demonstrate that high doses of both DMSO and its major in vivo metabolite, DMSO2, provide significant protection against the development of murine autoimmune lymphoproliferative disease. Possible mechanisms of protection are discussed.

PMID: 3489943 [PubMed - indexed for MEDLINE]

Oral developmental toxicity study of methylsulfonylmethane in rats.

Authors:

Magnuson BA
Appleton J
Ryan B
Matulka RA

Author Address: Burdock Group, 888 17th Street NW, Washington, DC, USA. bmagnuson@umd.edu

Source: Food Chem Toxicol. 2007, Jun; 45(6):977-84. [Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association]

Abstract:

Methylsulfonylmethane (MSM) is a metabolite of dimethyl sulfoxide, and occurs naturally at low levels in many foods. MSM has received wide attention as a dietary supplement to promote joint health. The objective of these studies was to determine the developmental toxicity potential of MSM when administered orally to pregnant rats during the period of major organogenesis and histogenesis. In a preliminary dose-finding study, distilled MSM microprill (i.e., microspherical pellets of MSM) was administered by oral gavage at dose levels of 0 (vehicle control), 50, 250, 500, and 1000 mg/kg/day to 8-9 sperm-positive female Sprague-Dawley rats/group/day on gestation days 6-20. No evidence of maternal or fetal toxicity was observed. For the definitive developmental study, four groups of 24-25 timed-bred primiparous female rats were administered 0, 50, 500, or 1000 mg MSM/kg/day via gavage on gestation days 6-20. Maternal feed consumption, body weight, body weight gain, uterus weight and corrected body weight/body weight gain were unaffected by treatment. No evidence of maternal toxicity, and no significant differences in litter viability, litter size, or litter body weight were detected. Fetal evaluations failed to show any biologically significant increase in the incidence of anomalies in the MSM treated groups, and no malformations were seen in any of the fetuses. No evidence of fetal mortality, alterations to growth, or structural alterations were observed in the fetuses of dams administered 50-1000 mg/kg/day. Therefore, under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity was 1000 mg/kg/day.

Medical Subject Headings (MeSH):

Animals
Body Weight/drug effects
Dietary Supplements/*toxicity
Dimethyl Sulfoxide/*toxicity

Eating/drug effects
Female
Fetal Development/*drug effects
Fetus
Litter Size/drug effects
Male
Maternal Exposure
No-Observed-Adverse-Effect Level
Organ Size/drug effects
Organogenesis/*drug effects
Pilot Projects
Pregnancy
Random Allocation
Rats
Rats, Sprague-Dawley
Sulfones/*toxicity

CAS Registry Numbers:

Sulfones (0)
Dimethyl Sulfoxide (67-68-5)
dimethyl sulfone (**67-71-0**)

Language: English

International Standard Serial Number: 0278-6915 (Print)

Publication Types:

Journal Article

Entry Month: June, 2007

Title Abbreviation: Food Chem Toxicol

Year of Publication: 2007

Last Revision Date: April 6, 2007

Medline Citation: NLM

Country: England

Citation Subset: IM

Medline Title Abbreviation: Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association

Article Date: 20061213

Stat: MEDLINE

Document Number: medline/17258373

DIMETHYL SULPHONE
CASRN: 67-71-0
For other data, click on the Table of Contents

Substance Identification:

Substance Name: DIMETHYL SULPHONE

CAS Registry Number: 67-71-0

Data Type:
Mutagenicity

Studies Data:

Mutagenicity Studies:

Test System:	AMES SALMONELLA TYPHIMURIUM
Strain Indicator:	TA98
Metabolic Activation:	NONE
Method:	PREINCUBATION
Dose:	0.003-300 UMOL/PLATE (TEST MATERIAL SOLVENT: WATER)
Results:	NEGATIVE
Reference:	

[AESCHBACHER,HU, WOLLEB,U, LOLIGER,J, SPADONE,JC AND LIARDON,R; CONTRIBUTION OF COFFEE AROMA CONSTITUENTS TO THE MUTAGENICITY OF COFFEE; FOOD CHEM. TOXICOL. 27(4):227-232, 1989]

Test System:	AMES SALMONELLA TYPHIMURIUM
Strain Indicator:	TA100
Metabolic Activation:	NONE
Method:	PREINCUBATION
Dose:	0.003-300 UMOL/PLATE (TEST MATERIAL SOLVENT: WATER)
Results:	NEGATIVE
Reference:	

[AESCHBACHER,HU, WOLLEB,U, LOLIGER,J, SPADONE,JC AND LIARDON,R; CONTRIBUTION OF COFFEE AROMA CONSTITUENTS TO THE MUTAGENICITY OF COFFEE; FOOD CHEM. TOXICOL. 27(4):227-232, 1989]

Test System:	AMES SALMONELLA TYPHIMURIUM
Strain Indicator:	TA102
Metabolic Activation:	NONE
Method:	PREINCUBATION
Dose:	0.003-300 UMOL/PLATE (TEST MATERIAL SOLVENT: WATER)
Results:	NEGATIVE
Reference:	

[AESCHBACHER,HU, WOLLEB,U, LOLIGER,J, SPADONE,JC AND LIARDON,R; CONTRIBUTION OF COFFEE AROMA CONSTITUENTS TO THE MUTAGENICITY OF COFFEE; FOOD CHEM. TOXICOL. 27(4):227-232, 1989]

Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA98
Metabolic Activation: RAT, LIVER, S-9, AROCLOR 1254
Method: PREINCUBATION
Dose: 0.003-300 UMOL/PLATE (TEST MATERIAL SOLVENT: WATER)
Results: NEGATIVE
Reference:

[AESCHBACHER,HU, WOLLEB,U, LOLIGER,J, SPADONE,JC AND LIARDON,R; CONTRIBUTION OF COFFEE AROMA CONSTITUENTS TO THE MUTAGENICITY OF COFFEE; FOOD CHEM. TOXICOL. 27(4):227-232, 1989]

Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA100
Metabolic Activation: RAT, LIVER, S-9, AROCLOR 1254
Method: PREINCUBATION
Dose: 0.003-300 UMOL/PLATE (TEST MATERIAL SOLVENT: WATER)
Results: NEGATIVE
Reference:

[AESCHBACHER,HU, WOLLEB,U, LOLIGER,J, SPADONE,JC AND LIARDON,R; CONTRIBUTION OF COFFEE AROMA CONSTITUENTS TO THE MUTAGENICITY OF COFFEE; FOOD CHEM. TOXICOL. 27(4):227-232, 1989]

Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA102
Metabolic Activation: RAT, LIVER, S-9, AROCLOR 1254
Method: PREINCUBATION
Dose: 0.003-300 UMOL/PLATE (TEST MATERIAL SOLVENT: WATER)
Results: NEGATIVE
Reference:

[AESCHBACHER,HU, WOLLEB,U, LOLIGER,J, SPADONE,JC AND LIARDON,R; CONTRIBUTION OF COFFEE AROMA CONSTITUENTS TO THE MUTAGENICITY OF COFFEE; FOOD CHEM. TOXICOL. 27(4):227-232, 1989]

Administrative Information:

CCRIS Record Number: 2938

Last Revision Date: 20080314

Update History:
Complete Update on 2008-03-14
Complete Update on 10/01/1991, 6 fields added/edited/deleted.

[redacted]

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

3.1 Methylsulfonylmethane / dimethyl sulfone - submission 2/3

Dear Secretariat

[redacted] **Submission – Methylsulfonylmethane (MSM)**

Thank you for the opportunity for the complementary healthcare industry to provide comment on the proposed scheduling of **Methylsulfonylmethane (MSM)** for consideration by the Joint meeting of the Advisory Committees on Medicines and Chemicals Scheduling (ACMS and ACCS).

[redacted]

[redacted] notes that the current proposal for MSM is in regard to its consideration for inclusion into Schedule 4 for human therapeutic use in concentrations greater than **1500 mg per dosage unit**. This consideration may also include methylsulfonylmethane for non-human use, mirroring the scheduling of dimethyl sulfoxide.

As a side note, [redacted] *recommends that the any reference to this substance be consistent with the TGA Australian Approved Name (AAN) - 'dimethyl sulfone' to reduce misunderstanding by sponsors.*

[redacted] provides the following comments for consideration:

[redacted] acknowledges the proposal for MSM originates from the fact that a substance may be captured by another entry as a derivative of that substance. MSM can be prepared by oxidation of dimethyl sulfoxide (DMSO) with hydrogen peroxide which suggests that MSM could be classified as a derivative of DMSO and therefore captured by the schedule entries for DMSO.

[redacted] notes that the provisions in Part 1 (2) (j) of the *Standard for Uniform Scheduling of Medicines and Poisons* (SUSMP) state that any other substance included in Schedules 1 to 6, at a concentration not exceeding 10 mg per litre or 10 mg per kilogram, unless that substance is also included in Schedule 7 or 8, **is excluded**. However, the monograph for MSM in the United States Pharmacopoeia has a limit of 0.1% (greater than the exclusion limits for inclusion into the SUSMP); [redacted] assumes this is the reason behind the proposal for inclusion of an entry for MSM.

Noting the above, [redacted] strongly **opposes** a new entry for MSM into Schedule 4 based on the following:

- MSM has been evaluated and approved for eligibility as a Listable active ingredient with no daily dosage limit - refer to Listing Notice 2008 (No. 6). It should be noted that this substance was previously assessed by IJEACM[1] (refer to Item 3.5 April 2006 meeting). In addition, IJEACCM also evaluated DMSO (refer to Item 3.6 July 2006 meeting) where it was concluded that '*limited pre-clinical and clinical data suggests that oral and topical toxicity of DMSO is relatively low in humans, even after repeated administration'*. Both evaluations considered quality and safety of the substance for use as a listable ingredient. The collective outcome determined that there was **no safety basis for restricting MSM based on daily dosage.** [redacted] therefore questions the justification for including a restriction on the substance.

- The Methylsulfonylmethane USP monograph (synonym dimethyl sulfone) specifies that '*not more than 0.1% of dimethyl sulfoxide is found, not more than 0.5% of any other individual impurity is found; and the sum of all impurities, including dimethyl sulfoxide, is not more than 0.2%*'.

As a proposed solution, [redacted] recommends not including the proposed entry for MSM and instead suggests amending the entry for DMSO in Schedule 4 to exclude Dimethyl sulfone when compliant with the MSM (dimethyl sulfone) monograph in the USP.

[redacted] would welcome the opportunity to discuss any matters relating to this submission and if you require further information please do not hesitate to contact me.

Yours sincerely

[redacted]

19 January 2011

[1] IJEACCM was a Committee established under the proposed Trans-Tasman Harmonisation process which included representatives from the Therapeutic Goods Administration in Australia and Medsafe in New Zealand; all of which were technical and regulatory experts.

3.1 Methylsulfonylmethane / dimethyl sulfone - submission 3/3

Submission to Joint meeting of the Advisory Committees on Medicines and Chemicals Scheduling (ACMS and ACCS) regarding proposal below:

3.1 Methylsulfonylmethane - consideration of inclusion of methylsulfonylmethane in Schedule 4 for human therapeutic use in concentrations greater than 1500 mg per dosage unit. This consideration may also include methylsulfonylmethane for non-human use, mirroring the scheduling of dimethyl sulfoxide.

This submission is to recommend that products containing methylsulfonylmethane and used for oral administration to animals should not be included in Schedule 4.

Methyl-sulfonyl methane (MSM) is an organic sulphur-containing compound that occurs naturally in a variety of fruits, vegetables, grains and animals and serves as an important source of bioavailable sulphur. MSM is a volatile component in the sulphur cycle and a major dietary source of sulphur. MSM is readily soluble and contains 34% elemental sulphur. Sulphur is the third most abundant mineral based on the percentage of total body weight. The sulphur-containing amino acids are methionine, cysteine, cystine, homocysteine, homocystine and taurine. Compounds containing sulphur are found in all body cells and are indispensable for life. Sulphur is responsible for the conformation of body proteins through the formation of disulfide bonds, thereby holding connective tissue together. Sulfydryl groups are vital for the catalytic function of several body enzymes. To perform these roles, constant intake of assimilable sulphur is needed by the body.
MSM is used to improve condition of the hair, skin and nails, as MSM contributes sulphur to cystine, a sulphur amino acid required for keratin production (Richmond 1986).
Sulfur from MSM has been shown to be incorporated into sulphur amino acids in animals (Richmond 1986). MSM has been shown to be orally absorbed and the sulfur is biotransformed into a number of organo-sulfur molecules which are utilized in several reactions within the horse (Jones 2000).

MSM is recommended as a nutritional supplement for managing horses with osteoarthritis (Jones 2000). A study in equine cartilage showed arthritic cartilage had one-third the sulphur concentration of normal cartilage (Rizzo et al, 1995) and mice with arthritis given MSM, experience less joint deterioration (Murav'ev et al 1991). According to a preliminary report, a double-blind trial in people with osteoarthritis found that MSM, in the amount of 2,250 mg per day, reduced pain after six weeks (Lawrence 1998).

MSM has been found to improve hoof growth (Larkins 1996)

Oral dosage of MSM is in the range of 1-3g/day in humans (Monograph 2003). The suggested dose for MSM for arthritis treatment in horses is 10g/day (Jones, 2000).

MSM is currently present in a number of products registered by the APVMA. In many of these products MSM is not considered an active, it is considered as a sulfur supplement. Sulfur is part of the nutritional requirements of animals and is listed in the US National Research Council of the US National Academy of Sciences as a requirement for dogs and horses (Nutrient Requirements of Equine and Nutrient Requirements of Dogs). In order to be considered by the APVMA as a nutritional

supplement any vitamin, mineral or amino acid listed on the label must provide no less than 25 per cent of the daily requirement of that vitamin, mineral or amino acid for the nominated animal species and age/class of animal. The NRC requirement for maintenance of an adult horse is 12g of sulphur per day. MSM contains 34.06% of sulphur, thus to provide 3g-12g of sulphur for a horse (25%-100% of the nutritional requirement), the horse would require a dose of ~9-36g MSM/day.

The current proposal by the scheduling committee for any supplement providing greater than 1500mg (1.5g) of MSM daily to require scheduling as an schedule 4 would cause a number of currently open selling products to require scheduling as schedule 4, for supply only by veterinary prescription.

Toxicity

Methylsulfonylmethane (dimethyl sulfone or $DMSO_2$ with chemical formula $[CH_3]_2SO_2$) is of very low toxicity (Oral LD_{50} (rat): >17,000 mg/kg). In rats, no adverse events were observed after daily doses of 2 g MSM per kg of body weight. In a 90-day follow-up study rats received daily MSM doses of 1.5 g/kg, and no changes were observed in terms of symptoms, blood chemistry, or gross pathology (Horváth et al 2002). The lethal dose of the similar molecule dimethyl sulfoxide DMSO (chemical formula $[CH_3]_2SO$) in rats is over 20g/kg (Parcell 2002). It is apparent that MSM is a safe nutrient for animals.

Products registered with the APVMA which contain MSM:

APVMA no.	**Product Name**
56532	Joint Guard Powder for Horses
59927	NV Joint Guard Powder for Dogs
62059	NV Joint Guard Powder for Cats
62605	Rufus & Coco Joint Aid May Help Reduce Non-Infectious Joint Inflammation Powder Suitable For Dogs
62614	Outback Vet Joint Maintain Powder For Horses
62825	Outback Vet Joint Maintain Powder For Dogs
64745	Arthri Zing Joint Powder For Dogs
62683	Joint Guard Liver Chews For Dogs

There is one injectable product containing MSM registered with the APVMA

XXXXX

XXXXX

XXXXX

The above list demonstrates that there are a number of veterinary products, registered with the APVMA containing MSM, the majority of these products are registered under the ‘low risk’ category for use to maintain joint health. These products contain glucosamine and chondroitin sulfate as the main active constituents, these oral supplements do not currently require a veterinary prescription but are available direct to the public. It would not be appropriate to schedule MSM for oral administration to animals as a schedule 4 product as many of these products would then become

available only through veterinarians which would significantly add to the cost of the products as veterinarians typically increase the product price. Further Schedule 4 products, to be prescribed by a veterinarian are products which require a veterinary diagnosis. Minor problems, such as low grade joint problems, do not require a veterinarian to prescribe an oral supplement.

XXXXX

XXXXX

We argue that orally administered veterinary products such as XXXXX should not be classified as S4.

Please contact me if you require any further information or discussion

Best regards

XXXXX

XXXXX
XXXXX

XXXXX
XXXXX
XXXXX
XXXXX
XXXXX
XXXXX

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