# EDITED SUBMISSIONS RECEIVED IN RESPONSE TO THE NOTICE INVITING FURTHER SUBMISSIONS IN RELATION TO DELEGATES' INTERIM DECISIONS ON RECOMMENDATIONS FROM 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 42ZCZQ, 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 April 2011 Reasons for delegate's interim decisions (accessible at www.tga.gov.au/industry/scheduling-decisions-interim.htm).

This call for further submissions (as required under subsection 42ZCZP of the Regulations), invited comments from the applicant and parties who made a valid submission in response to the original invitation for comment. Please note that, for the February 2011 meetings, there was an additional supplementary original invitation notice. Both invitation notices, which had closing dates of 19 January and 21 January 2011 respectively, are accessible at www.tga.gov.au/newsroom/consult-scheduling-acmcs.htm.

In accordance with the requirements of subsection 42ZCZQ 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 was then 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 i.e. a request for material to be confidential did not automatically classify that material as confidential. The SPF is accessible at www.tga.gov.au/industry/scheduling-spf.htm.

Discrete submissions have been grouped by item. However, where submissions relate to multiple items, these will be separately grouped.

# LIST OF SUBMISSIONS

## 1. SUBMISSIONS ON INTERIM DECISIONS ARISING FROM RECOMMENDATIONS BY ACCS#1

No further submissions were received.

## 2. SUBMISSIONS ON INTERIM DECISIONS ARISING FROM RECOMMENDATIONS BY ACMS#2

| Item | Number of submissions |
|---|---|
| 2.1.2 Fexofenadine | 2 |
| 2.1.3 Ibuprofen | 1 |
| 2.1.4 Ibuprofen combined with paracetamol | 1 |
| 2.2.2 Pantoprazole | 1 |

## 3. SUBMISSIONS ON INTERIM DECISIONS ARISING FROM RECOMMENDATIONS BY ACCS-ACMS#2

No further submissions were received.

[redacted]

11 May 2011

# Comments by the [redacted] on the Delegate's Interim Decisions – April 2011

## Interim Decision

**FEXOFENADINE – Schedule 2 Amendment**

FEXOFENADINE in preparations for oral use except in preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

a. in a primary pack containing 10 dosage units or less; and

b. labelled with a recommended daily dose not exceeding 120mg of fexofenadine.

## [redacted] position

[redacted] does not support the interim decision to exempt small packs of fexofenadine from scheduling.

[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 Standard for the Uniform Scheduling of Medicines and Poisons (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 its meeting of 23 February 2011, the Advisory Committee on Medicine Scheduling (ACMS) considered a proposal to exempt small packs sizes of fexofenadine from scheduling for the treatment of allergic rhinitis. The Delegate of the Secretary to the Department of Health and Ageing (Delegate) has supported these recommendations as part of the interim decisions following this meeting.

# Quality Use of Medicines

Quality Use of Medicines (QUM) is one of the central objectives of Australia's National Medicines Policy[2]. [redacted] believes that QUM is best supported by the supply of medicines through a pharmacy with access to specialised professional support and advice from a pharmacist. As such, [redacted] have traditionally opposed exempting medicines from scheduling because [redacted] have been concerned that the proposed arrangements may facilitate use of the medicines in a manner that does not align with QUM principles. There are no controls or quality assurance processes in place for the supply of medicines through the grocery channel and grocery customers with chronic conditions can purchase one or one hundred small packs of these medicines without any question asked about the condition, the patient history or the use of the medicine.



[redacted]

# Key Points

a. Essential to facilitate triaging for health care professional intervention as chronic SAR or SAR with complications warrants investigation

b. Important to protect the most vulnerable patient groups, particularly the young, elderly, debilitated and people whose first language is not English

c. The inclusion of warnings and directions on packs does not surmount the issues associated with poor consumer health literacy without the opportunity for counselling

d. The risk factors associated with fexofenadine use warrant management through the pharmacy sector

e. Access through the pharmacy sector is more than adequate and provides access to health professional advice to support QUM objectives

# Comments

On reading the Delegate's reasons for interim decisions (Delegate's Reasons), it would appear the primary arguments to support the decision to exempt fexofenadine from scheduling under defined circumstances are:

1. Research data regarding the links between SAR and asthma warrants further investigation
2. Scheduling exemptions for other medicines with similar safety concerns provide a precedent
3. Chronic SAR sufferers are sufficiently informed for self-treatment
4. Availability through grocery channels allows greater access in urgent cases
5. Safety issues can be addressed by responsible packaging and labelling

With these reasons in mind and noting that the evaluator for the original application did not support a scheduling exemption for fexofenadine, [redacted] provides the following arguments for opposing the interim decision for a fexofenadine exemption:

**1. Research data regarding the links between SAR and asthma warrants further investigation**

1.1 In our original submission, we advised of the link between SAR and asthma and how National Asthma Council Guidelines[3] report that 20-30% of patients with known allergic rhinitis also have asthma and that patients can mistake symptoms of allergic rhinitis for asthma. We also advised of a 2006 European paper[1] reporting that 40-50% of patients with allergic rhinitis suffer from asthma and more than 90% of asthmatics also have rhinitis. Our concern was that with such a link and the burden of asthma on our community, it is essential that people suffering the symptoms of SAR are exposed as much as possible to health care professional intervention. Australia has the second highest incidence of asthma in the world and 40% of Australians have an allergic disease.[4]



[redacted]

In the Delegate's Reasons, it records the ACMS as noting 'the studies reported may have contained confounding data and a closer examination of the research was warranted'. This may be true and we would support further investigation, however, the current evidence should not be dismissed as being inconsequential as the consequences could be significant. Until further investigation is conducted, the information provided should be seriously considered and scheduling changes should not be implemented.

With this in mind, we suggest that the research to date indicates a link between asthma and SAR that warrants facilitating access to health professional intervention and that an exemption from scheduling for 5 days therapy of fexofenadine does not facilitate this access.

**2. Scheduling exemptions for other medicines with similar safety concerns provide a precedent**

2.1 In the Delegate's Reasons, the applicant is cited as using the exemption from scheduling for small pack sizes of paracetamol, aspirin and ibuprofen (p74) as justification to exempt products with a so-called 'better safety profile' such as fexofenadine. The applicant is also cited (p69) as identifying several products currently available through grocery outlets despite a B1, B2, C or D pregnancy category and/or restriction on use during breast-feeding and that the risk of use of these products in pregnancy and breast-feeding was managed via label warnings.

[redacted] believes it is a dangerous practice to introduce the idea of 'precedents' in the review of products for which an exemption from scheduling is being considered. There are no quality assurance processes for the supply through grocery outlets of products that are exempt from scheduling and each application must be considered on its own merits with regards to the use and safety profile of the medicine concerned. It is unknown how many, if any, potential problems there have been in the community from the use of these 'precedents' in pregnancy and breastfeeding due to their unrestricted access.

There is also nothing to indicate that should the exemption from scheduling for these 'precedents' be reconsidered, the use of warning labels to address significant safety concerns may not continue to be regarded as sufficient, particularly with the low level of health literacy in Australia now identified and documented.

2.2 The proposal is to exempt small packs (up to 5 days supply) of fexofenadine from scheduling for the short-term symptomatic relief of SAR in adults and children over 12 years of age as this will provide access to 'rescue packs' in a similar manner to that for ranitidine, paracetamol, aspirin or ibuprofen.

While we understand the argument to allow for the availability of so called 'rescue packs' of these medicines for minor ailments, we have concerns with the quantities available. 'Rescue packs' should be solely to provide short-term relief without delaying access to professional advice about the condition and the safe and appropriate use of any treatment. We suggest that a pack containing more than 24 hours therapy is not a 'rescue pack' and unrestricted access to such should be discouraged.

We note in the Delegate's Reasons that people suffering chronic conditions such as SAR would consult a health care professional for larger pack sizes. We suggest



[redacted]

this does not work in reality. Without controls in the grocery sector that limit the number of packs supplied to individuals, customers can purchase multiple packs to treat chronic conditions without any need to see a health care professional.

This becomes more of a concern as progress is made on the e-health agenda and systems better enable the recording of non-prescription medicine use against a person's medicine profile as well as that for prescribed medicines. Ideally, at some time in the future, it would be reasonable to hope that all treatments for chronic conditions such as SAR can be recorded against a patient's profile in a health care setting.

We believe the most appropriate manner to ensure that patients with chronic conditions have access to the most appropriate treatments and advice is to limit which medicines are exempt from scheduling, and to ensure those medicines that are exempt are in a pack size that supports the intent of the exemption and facilitates access to health care professional support. We fail to see justification for legitimate 'rescue packs' to contain more than 24 hours therapy.

**3. Chronic SAR sufferers are sufficiently informed for self-treatment**

3.1 We note the Omnibus survey reported in the Delegate's Reasons (p71) identified 37% of consumers presenting to the pharmacist do so as a result of self-diagnosis. This is a very small sample size to give weight to any decision to exempt fexofenadine from scheduling.

3.2 The Delegate's Reasons indicate that chronic SAR sufferers are already informed of the appropriate treatments for their condition and as such, are capable of managing their condition without the need to access health professional support.

While chronic SAR sufferers may be considerably aware of their condition, in line with QUM principles, they still benefit by having access to balanced, accurate, evidence-based, current advice about the most appropriate manner to manage their condition. Pharmacists are medicines experts and with access to the full range of therapies available, can recommend the most appropriate and cost-effective remedies as well as to triage and refer patients with symptoms warranting further investigation. Should chronic sufferers have other co-morbidities such as a respiratory tract infection, pharmacists are able to triage and also provide medical certificates if appropriate.

It is interesting to note the results from a recent survey[5] in the United States that included data on the treatment and prevention of allergy-related symptoms. Adult antihistamines accounted for only 32% of pharmacist recommendations. Other products recommended included:

- decongestants
- ophthalmic drops
- multi-symptom products
- expectorants
- breathe-right strips

The survey identifies the strength of facilitating pharmacist intervention:

- pharmacists are the most accessible health care providers



[redacted]

- as the medicine experts, pharmacists are trained in both prescription and over-the-counter medicines
- pharmacists can provide patients with important information about how medicines may interact with certain foods, other medicines and dietary supplements
- pharmacists can help patients select products that address the patient's individual needs
- pharmacists can help patients to navigate their way through the various products available

3.3 In our original submission, we argued that 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.[6] Anecdotal reports from pharmacists indicate that the 2010/2011 SAR season has been particularly bad and there has been an increase in the number of consumers who are finding that 'conventional antihistamine therapy' has been insufficient to control the symptoms. Advice about alternative therapies is not available from the grocery sector.

3.4 In considering exempting fexofenadine from scheduling, in addition to increasing availability for people who may be familiar with SAR and/or the use of antihistamines as a treatment, there will be increased access for people who are unfamiliar with SAR and ignorant of the most appropriate treatments.

It is interesting to note the assumption recorded in the Delegate's Reasons (p83) that 'patients with no history of SAR who experience a first attack would present to a pharmacy for appropriate advice where there would be access to the full range of available treatments'. This may be the ideal, but realistically, with access through the grocery channels, it is more reasonable to expect increased advertising and marketing tactics to promote availability from supermarkets and to prompt consumers to purchase this medicine without advice or access to health professional support.

Grocery outlets arrange promotional displays to prompt purchase, with companies paying premiums to have promotional stands positioned to maximise spontaneous purchase. In fact, chronic SAR sufferers may be more aware of the limitations of the oral anti-histamines and less likely to rely solely on oral antihistamine therapy. It would be logical to expect the grocery channel to develop a market by targeting people who are unfamiliar with the condition and/or the availability of alternative treatments. Even though the intent of the exemption from scheduling is for 'the short-term symptomatic relief of SAR in adults and children over 12 years of age', unrestricted access to 5 day packs does not necessarily support 'short-term relief' as grocery customers can purchase multiple packs as frequently as they wish without any questions asked.

3.5 In a grocery setting, it is more than likely that fexofenadine products will be juxtaposed with oral and topical nasal decongestants as well as decongestant eye drops. Patients familiar and unfamiliar with SAR who have nasal and ophthalmic symptoms could easily select additional products such as decongestant nose drops or eye drops to help their symptoms which may be inappropriate. There will be no advice available about the appropriateness of the selection or how to



[redacted]

use these products. No advice about possible rebound congestion. No advice on alternative products that would be more appropriate.

3.6 We also do not believe it is cost-effective for consumers to purchase something from a grocery outlet to trial, and then to consult a pharmacist if the product does not work. Consumers should be provided with the necessary information to make an informed choice as to what treatment is most appropriate.

**4. Availability through grocery channels allows greater access in urgent cases**

4.1 When medicines are available through the grocery channel, there are no controls for supply. Consumers can purchase multiple packs without any questions asked. It would be an interesting study to examine the supply of products containing ranitidine, paracetamol, aspirin or ibuprofen through grocery channels and investigate the incidence of single-pack versus multiple-pack purchase. An Irish study that investigated the purchase of paracetamol in non-pharmacy outlets in quantities of either 2 x 24 packs or 4 x 12 packs demonstrated that purchases were made in each outlet without difficulty or questions from sales assistants, even though there was commentary on the researcher's presumed poor health.[7]

4.2 We note that one of the submissions recorded in the Delegate's Reasons (p80) states ' that both pharmacy and grocery sectors share the responsibility for patient management, where the grocery sector has played an important role in assisting Australian consumers to manage a variety of conditions such as headaches, general pain, coughs and colds, heartburn and smoking cessation' This is a very interesting statement as the grocery sector also assumes the main responsibility for supply products to cause or aggravate many of these conditions: cigarettes, alcohol, processed foods. Their role is 'supply without any responsibility'.

4.3 The applicant claims that 'the desired outcome of a 5 day/low dose fexofenadine course is for short term symptomatic control and not allergy therapy' (p74). This may be the intent of the Delegate's decision but there is no way to control it. With unregulated access through grocery channels, consumers can access fexofenadine for any condition.

[redacted] is particularly concerned that some consumers who suffer severe allergic reactions may indeed consider accessing the 'antihistamine available through grocery' instead of seeking urgent medical intervention, particularly if there is increased advertising and in-store promotional campaigns. What happens if a person has a serious allergic reaction that warrants urgent medical attention? Could this decision facilitate self-treatment? Is there a possibility that they may go to the supermarket and purchase a pack of fexofenadine to treat a potentially serious event because it is 'an antihistamine' and 'antihistamines are used for allergies'? Will adequate labelling mitigate this risk?

- In our original submission, we argued that there are over 5000 pharmacies around Australia, including rural and remote locations, and many pharmacies operate 7 days a week with extended trading hours. We provided details on the opening hours of Canberra pharmacies as a general example but it seems there remains a false view that the grocery sector provides greater access than community pharmacy. In fact, in some jurisdictions, regulations for store trading hours mean that after-hours pharmacy access is as good as or better than that through the grocery sector.



[redacted]

As an example, a recent analysis of access in metropolitan areas showed:

- In Western Australia, pharmacy has no restricted trading hours as it is a 'specialty retail store'. There is a majority of pharmacies operating 7 days a week and 2 pharmacies open for 24 hours a day. In contrast, supermarkets have restricted trading hours and can open until 9pm Monday to Friday, until 6pm on Saturday, and cannot trade on Sunday.

- In Melbourne, there are 2 pharmacies that are open for 24 hours a day and many operating 7 days a week. By comparison, there are only 4 Coles and no Woolworths supermarkets that are open for 24 hours a day.

- In Brisbane, there are no pharmacies or supermarkets that open for 24 hours a day. There are 3 pharmacies that open until 11pm and many operating 7 days a week. There are restrictions on trading hours for supermarkets which can open on weekdays until 9pm and till 6pm on weekends.

In addition, we note that in country areas, pharmacists generally provide after-hours access for 'urgent cases'. This is something that does not happen through the grocery sector.

4.4 We also question the decision that 'urgent treatment' requires 5 days worth of therapy. Should 'rescue therapy' be in the public interest, there should be no more than 24 hours worth of therapy so as to facilitate access to professional intervention and to minimise adverse events from inappropriate use.

## 5. Safety issues can be addressed by responsible packaging and labelling

5.1 We note that the committee has agreed with the applicant's assertion that the key to safe and efficacious use of medicines that are exempt from scheduling is responsible labelling that addresses the known areas of potential concern. In an ideal world, this would be true. However, health literacy is a serious issue and we are concerned that not only do people not read the labels, but when they do, they often don't understand what they are reading.

A survey[8] conducted by the Australian Bureau of Statistics (ABS) identified 46% of Australians aged 15 to 74 years as not having sufficient literacy skills to meet the complex demands of everyday work and life, and that on the health scale, 60% attained scores below the minimum requirement to meet everyday needs. The ABS survey also identified that only 36% and 38% of people whose language was not English attained scores at or above the level that demonstrated sufficient prose and document literacy respectively to meet everyday needs.

Worryingly, 52% of survey respondents in the 15 to 19 years of age group demonstrated literacy levels below the standard and people who were less educated or from lower socio-economic areas performed more poorly. It is essential that the most vulnerable members of society are protected. With reference to the Delegate's Reasons (p74), the applicant claimed that with revised warning statements, safety concerns about pregnancy and breast-feeding are adequately addressed. With consideration of the ABS statistics, we suggest that poorly educated young girls from lower socio-economic areas who are pregnant or breast-feeding may not benefit from 'adequate labelling'. It is vulnerable groups such as this that must have access to health professional advice.



[redacted]

5.2 We note in the Delegate's Reasons (p69) the statement by the applicant that 'in relation to misdiagnosis, the most likely outcome was a lack of symptom relief leading to a discontinuation of therapy and the patient seeking professional advice'. While this is one possible scenario, there is also a possibility that a patient with a more ominous condition may have sufficient relief to continue purchasing multiple packs through the grocery supply without any need to seek professional advice. By purchasing small packs (contrary to the intent for the scheduling exemption), the patient could delay seeking medical advice for a serious condition until symptoms deteriorate. Or there may simply be more effective and/or more cost-effective therapies available through a pharmacy of which the consumer is not aware.

5.3 We also note in the Delegate's Reasons (p75) that the applicant references a revised Consumer Medicine Information (CMI) leaflet. While an updated CMI is applauded, how do grocery consumers access the CMI? These are usually not within the pack, or is the applicant's intent to include a CMI in every pack? If so, will this be a requirement for all sponsors?

# 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. SAR is a condition that should be managed with professional support.

[redacted] does not support the Delegate's interim decision to exempt small packs of up to 5 days therapy of fexofenadine from scheduling. If a 'rescue pack' is deemed to be of benefit to the Australian public, [redacted] suggests the quantity should be no more than 24 hours therapy as a means to promote QUM and facilitate access to health care professional advice.

**Reference Sources:**


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

[2] http://www.health.gov.au/internet/main/publishing.nsf/Content/National+Medicines+Policy-1

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

[4] http://www.nationalasthma.org.au/content/view/177/26/

[5] American Pharmacists Association; Pharmacists offer guidance on top over-the-counter medicines; 25 April 2011; http://www.pharmacist.com/AM/PrinterTemplate.cfm?Section=Newsroom&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=25906

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

[7] Laffoy M, Scallan E, Byrne G; Paracetamol Availability and Overdose in Ireland; 2000; http://www.lenus.ie/hse/handle/10147/46666

[8] ABS 4228.0 – Adult Literacy and life Skills Survey, Summary Results, Australia, 2006 (Reissue); www.abs.org.au




[redacted]

[redacted]

## 2.1.2 Fexofenadine - further submission 2 of 2.

**SUBMISSION TO THE ADVISORY COMMITTEE ON MEDICINES SCHEDULING IN RESPONSE TO THE APRIL 2011 INVITATION FOR FURTHER SUBMISSIONS ON THE DELEGATE'S INTERIM DECISIONS**

### PURPOSE

1. [redacted] makes this submission in response to a notice under subsection 42ZCZP of the *Therapeutic Goods Regulations 1990*, specifically the April 2011 invitation to provide further submissions on the Delegate's interim decisions on items from the February 2011 meeting of the Advisory Committee on Medicines Scheduling (ACMS). [redacted] provides comments on the interim decision on fexofenadine.

### RECOMMENDATIONS

2. In the absence of new evidence to support an exemption from scheduling for fexofenadine, [redacted] is firmly opposed to the interim decision. [redacted] believes the existing entry of fexofenadine in Schedule 2 remains appropriate.

### FEXOFENADINE

3. [redacted] notes that this is the third occasion in less than two years that a request to exempt fexofenadine from scheduling has been considered by the scheduling committee (NDPSC/ACMS). While the recommended requirement for inclusion of a warning statement that the product should not be used by pregnant or breastfeeding women is new, [redacted] is not aware of any new evidence or information that would support an exemption from scheduling.

4. As outlined in [redacted] submission to the February 2011 ACMS meeting, seasonal allergic rhinitis (SAR) is a common condition which consumers can recognise and is suitable for short-term, self-treatment. Consumers are also generally aware that effective products to manage the symptoms of SAR are available through community pharmacies.

5. [redacted] believes better access to a medicine must be implemented in the context of appropriate opportunities for consumers to seek information or advice on the use of that medicine. In the case of fexofenadine, [redacted] would re-iterate that professional intervention would be appropriate at the time of supply of the product (eg. to provide information and counselling; to investigate instances when other causes (eg. an infection or more acute illness) may be suspected; to refer to a medical practitioner) or for advice on follow-up when original symptoms have not resolved after a few days. [redacted] believes supply of fexofenadine from an environment that does not afford this opportunity is not consistent with promoting quality use of medicines and therefore, not in the best public interest.

6. Access to non-prescription medicines from community pharmacies where professional intervention is available has been shown to help avoid adverse events and further costs to the health care system.[1] [redacted] firmly believes fexofenadine should not be exempted from scheduling requirements.

### SUMMARY

7. [redacted] believes the current Schedule 2 entry for fexofenadine remains appropriate and is firmly opposed to the interim decision to exempt fexofenadine from scheduling.

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[1] Williams KA et al. Non-prescription medicines and Australian community pharmacy interventions: rates and clinical significance. Int J Pharm Pract (2011). Doi: 10.1111/j.2042-7174.2010.00091.x

**Submitted by:**

[redacted]

11 May 2011

**2.1.3 Ibuprofen - further submission 1 of 1.**

[redacted]

11 May 2011

Medicines & Poisons Scheduling Secretariat (MDP88)
GPO Box 9848
Canberra ACT 2601
Email: SMP@health.gov.au Fax: 02-6289 2500

**Re: Comment on the interim decisions & reasons for decisions regarding item 2.1.3 ibuprofen – increase the maximum allowable amount of ibuprofen in liquid preparations in Schedule 2 from 4 g to 8g**

[redacted] welcomes the delegate's interim decision to amend the entry for ibuprofen under Schedule 2 of the SUSMP to allow a maximum total quantity of 8 grams of ibuprofen per pack of liquid formulation.

The decision was supported by the Expert Advisory Committee who recommended increasing the maximum allowable amount of ibuprofen in liquid preparations in Schedule 2 from 4 g to 8 g. The Committee also recommended an implementation date of no more than 6 months following the delegate's final decision (earliest 1 September 2011).

With regard to matters in section 52E of the Therapeutic Goods Act, [redacted] particularly supports the delegate's recommendation based on the following:

**Toxicity and safety**
The safety characteristics of ibuprofen are well known and there is a long history of safe use in Australia. Pharmacovigilence data have demonstrated a low potential for abuse and a low rate of serious adverse events following overdose.

Ibuprofen has a very wide therapeutic index and a lower potential for toxic effects at doses up to 200-400mg/kg.

**Risks**
The most frequently reported adverse events are gastrointestinal symptoms and serious gastrointestinal effects, particularly upper GI bleeding and these are less common with ibuprofen than with other NSAIDs.

[redacted]

The risk of accidental poisoning is unlikely to increase with the increased maximum quantity supported in the proposed Scheduling change and is minimised by child-resistant closures, clear dosing instructions by age and weight, the provision of measuring devices for accurate dose measurement and label warnings.

**Other considerations**

**Consistency with the maximum quantity allowed in divided dose preparations and with other Schedules**

A 4 gram limit for liquid ibuprofen formulations is considerably lower than for Schedule 2 packs of divided solid dosing forms with a maximum quantity per pack of 20 grams (100 x 200 mg).

In addition, despite its potential toxicity there is no size restriction on paracetamol liquid preparations in Schedule 2.

[redacted] looks forward to this decision being made final at the forthcoming meeting of the ACMS in June 2011.

Yours sincerely

[redacted]

**2.1.4 Ibuprofen+paracetamol**
**- further submissions 1 of 1.**

[redacted]

11 May 2011

The Secretary Fax: 02-6289 2500
Medicines & Poisons Scheduling,
Office of Chemical Safety and Environmental Health (MDP 88)
GPO Box 9848, Canberra ACT 2601
Email: smp@health.gov.au

**Re: Comment on the interim decisions & reasons for decisions regarding item 2.1.4 . Invitation for Public Comment**

[redacted] would like to submit comment in relation to the interim decision of the ACMS on the scheduling of ibuprofen 200 mg and paracetamol 500 mg combination. This is to be discussed at the forthcoming meeting of the ACMS in June 2011.

**2.1.4 IBUPROFEN COMBINED WITH PARACETAMOL**

**EXPERT ADVISORY COMMITTEE RECOMMENDATION**

*The committee recommended that the combination ibuprofen+paracetamol preparations currently captured by Schedule 2 (up to 200mg ibuprofen and 500mg paracetamol) be included in Schedule 3 in packs of 30 dosage units or less. The Committee recommended that the combination ibuprofen+paracetamol in packs of more than 30 dosage units be captured by Schedule 4.*

*The Committee recommended an implementation date of 1 September 2011 (three months following the delegate's final decision).*

**BACKGROUND**

This ibuprofen+paracetamol combination was previously considered by the NDPSC in June 2010. [redacted] notes " *The Committee agreed that the current scheduling of ibuprofen and paracetamol remained appropriate i.e. 200mg or less of ibuprofen in combination with 500mg or less of paracetamol, in packs of not more than 100 dosage units, remain Schedule 2".* **The conclusion of this meeting was that "no strong argument had been presented for changing the current scheduling".**

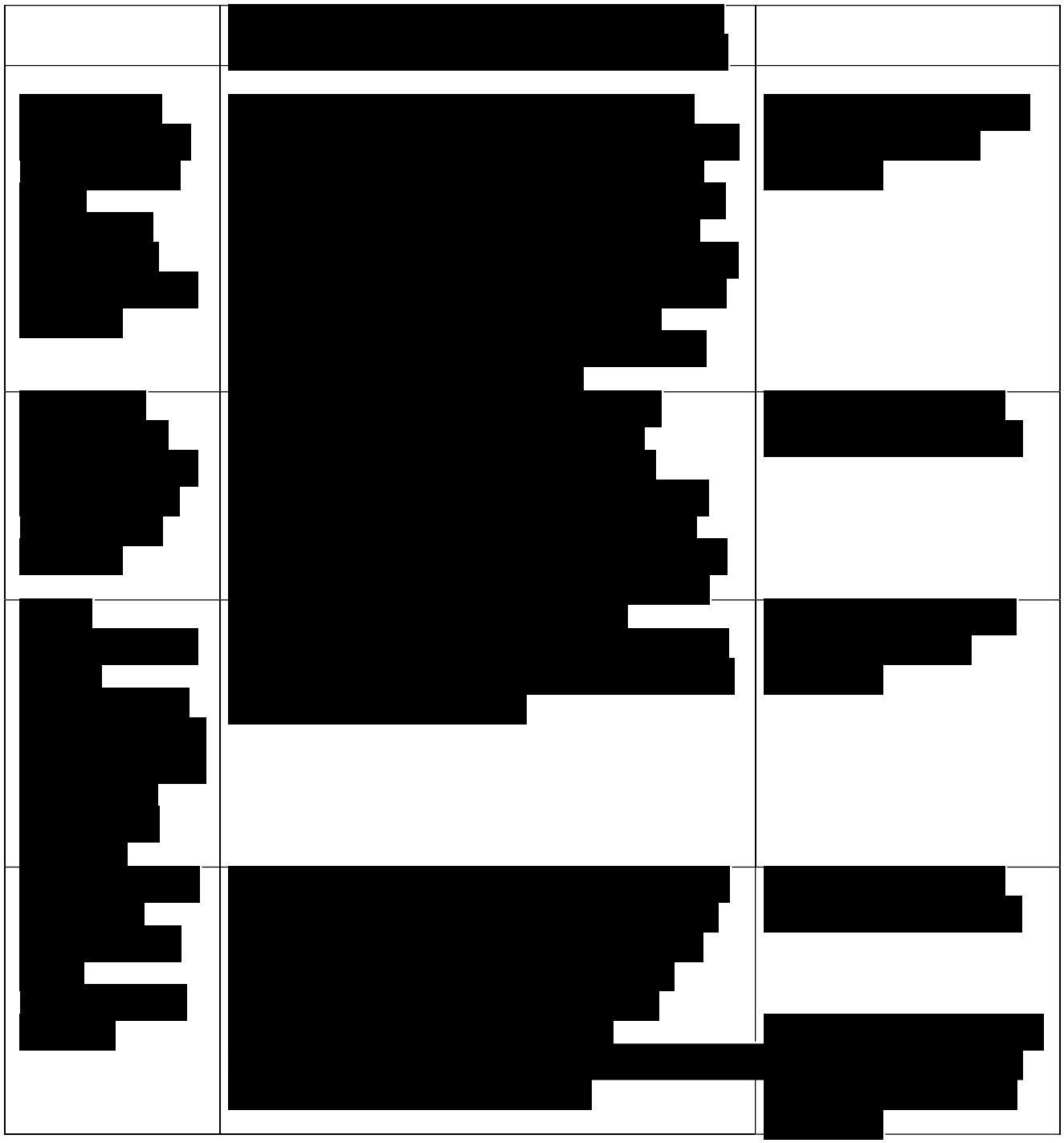
[redacted]

Since the June 2010 NDPSC m eeting, an identi cal product under the tradenam e 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 that can be advertised to the public. This com bination was also approved in Poland in December 2010.

Following dissolution of NDPSC i n July 2010, the delegate referred the proposal from the Advisory Comm ittee o n non-prescription Med icines (ACNM) to the Advisory Comm ittee o n Medicines Scheduling (ACMS) to reconsider the scheduling of the combination. In summary, the ACNM were recomm ending consideration of Schedule 3 or higher for the ibuprofen+paracetamol combination.

[redacted] believes the m ore conservative view now be ing taken b y the Comm itttee appe ars to be in relation to the issues presented by the ACNM. These are s ummarised in Table 1 b elow. [redacted] would now like to take the opportunity to address each of these issues.

[redacted]



**END OF COMMERCIAL IN CONFERENCE SECTION UNLESS IN BOLD**

**OVERALL BENEFITS OF THE PRODUCT**

***1) Alternative to OTC codeine combination products***

Since early 2010, all OTC com bination analgesics containing codeine (CACC) have been removed from Schedule 2 (S2) to either S3 or S4 leaving consum ers 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.

[redacted] 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 of the two actives. 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 product offers clinically proven combination analgesic efficacy utilising well-known, well-characterised, actives. This is in contrast to codeine containing combinations where positive clinical efficacy data on the contribution of codeine at non-prescription doses may be limited.

The product is not associated with the unpleasant side effects caused by codeine, e.g., nausea, constipation, dizziness. It is also not associated with the potential for addiction.

***2) Effective analgesia which is active-sparing***

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.

***3) Simplification of treatment***

The product offers simplification of therapy for those Pharmacists who are currently recommending the combination of ibuprofen and paracetamol for effective control of pain not relieved by the individual actives.

In summary, [redacted] believes this combination provides a safer alternative than codeine combination analgesics when used as directed. [redacted]

This combination should remain as currently scheduled.

**SUMMARY OF ISSUES UNDER SECTION 52E**

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

[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

(*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. [redacted] 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.

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 [5]. 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 benefit 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.

***(c) the toxicity of a substance***

[4] http://www.asmi.com.au/consumer/Self-Care-Products.aspx accessed 10/1/11
[5] 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

Both ibupro fen and paracetam ol have well-docum ented safety profiles. There is a low and well-characterised incid ence 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 an algesics and the contra-i ndications and warning on pack are fa miliar to them. The packaging and labelling of the combin ation tab let u tilise th e sam e warnings an d contra-indications and will ther efore be fa miliar. In additio n, at the proposed m aximum dail y dose there is a reduction in the daily amount of both ibuprofen and paracetam ol taken with the combination product, as opposed to the maximum daily dose of the individual components.

The grea test poten tial f or harm with the com bination lies in the pote ntial f or un intentional overdose due to consum er confusion regarding th e constituents of the com bination. In this respect ibuprofen 200 mg/paracetamol 500 mg tablet is no different from any other combination of si mple a nalgesics. To m inimise the risk of this occurr ing [redacted] undertakes to provide clear communication on p ack and in edu cational and pr omotional m aterial 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 [redacted].

[redacted]

***(e) the potential for abuse of a substance***

To date, there is no evidence that eith er paracetamol or ibuprofen is asso ciated with dependency, abuse or illicit use as individual actives. As a com bination, it is therefore expected that ibuprofen 200 mg/paracetamol 500 mg tablet w ill no t prod uce dependency. The lik elihood of abuse, m isuse and illicit use is low. In fact, in this reg ard the com bination of fers signif icant benefits over analgesic products containing codeine, which may produce dependence and are open to abuse.

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

Since the UK MHRA has classified the ibuprofen and paracetamol combination as a Pharmacy-Only M edicine[2] with adv ertising, [redacted] r equests the ACMS to con sider m aintaining th e 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

[redacted]

[redacted]

[redacted]

Section Editor: **Spencer S. Liu**

# Combining Paracetamol (Acetaminophen) with Nonsteroidal Antiinflammatory Drugs: A Qualitative Systematic Review of Analgesic Efficacy for Acute Postoperative Pain

Cliff K. S. Ong, PhD,* Robin A. Seymour, PhD,† Phillip Lirk, MD,‡ and Alan F. Merry, MBChB, FANZCA, FPMANZCA, FRCA§

**BACKGROUND:** There has been a trend over recent years for combining a nonsteroidal antiinflammatory drug (NSAID) with paracetamol (acetaminophen) for pain management. However, therapeutic superiority of the combination of paracetamol and an NSAID over either drug alone remains controversial. We evaluated the efficacy of the combination of paracetamol and an NSAID versus either drug alone in various acute pain models.

**METHODS:** A systematic literature search of Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and PubMed covering the period from January 1988 to June 2009 was performed to identify randomized controlled trials in humans that specifically compared combinations of paracetamol with various NSAIDs versus at least 1 of these constituent drugs. Identified studies were stratified into 2 groups: paracetamol/NSAID combinations versus paracetamol or NSAIDs. We analyzed pain intensity scores and supplemental analgesic requirements as primary outcome measures. In addition, each study was graded for quality using a validated scale.

**RESULTS:** Twenty-one human studies enrolling 1909 patients were analyzed. The NSAIDs used were ibuprofen ($n = 6$), diclofenac ($n = 8$), ketoprofen ($n = 3$), ketorolac ($n = 1$), aspirin ($n = 1$), tenoxicam ($n = 1$), and rofecoxib ($n = 1$). The combination of paracetamol and NSAID was more effective than paracetamol or NSAID alone in 85% and 64% of relevant studies, respectively. The pain intensity and analgesic supplementation was 35.0% ± 10.9% and 38.8% ± 13.1% lesser, respectively, in the positive studies for the combination versus paracetamol group, and 37.7% ± 26.6% and 31.3% ± 13.4% lesser, respectively, in the positive studies for the combination versus the NSAID group. No statistical difference in median quality scores was found between experimental groups.

**CONCLUSION:** Current evidence suggests that a combination of paracetamol and an NSAID may offer superior analgesia compared with either drug alone. (Anesth Analg 2010;110:1170–9)

Different classes of analgesics exert their effects through different mechanisms. Their side effects (e.g., respiratory depression with opioids or enteropathy with nonsteroidal antiinflammatory drugs [NSAIDs]) tend to be different and may be dose related. A combination of analgesics from different classes may provide additive analgesic effects with fewer side effects than when a single therapeutic drug is used. There has been a trend over recent years for combining NSAIDs with paracetamol (acetaminophen) for the management of acute postoperative pain,[1,2] but the therapeutic superiority of the combination over either drug alone remains controversial.[3,4] In 2002, Hyllested et al.[5] noted that paracetamol/NSAID combinations showed superior pain relief over paracetamol alone in 5 of 7 studies, but over an NSAID alone in only 2 of 4 studies, whereas Rømsing et al.[2] noted an advantage for such combinations over paracetamol alone in 6 of 9 studies but over an NSAID alone in only 2 of 6 studies. These authors noted that relevant studies were sparse. We have updated these reviews to include randomized controlled trials (RCTs) published since then with the aim of evaluating whether paracetamol/NSAID combinations provide superior efficacy in the treatment of acute postoperative pain to either drug alone.

## EVIDENCE IN HUMAN CLINICAL STUDIES FOR THE USE OF PARACETAMOL/NSAID COMBINATIONS

We aimed to determine whether paracetamol/NSAID combinations provide superior efficacy in the treatment of acute postoperative pain to either drug alone.

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## METHODS

A broad free-text search restricted to RCTs in English was undertaken in Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and PubMed, from January 1988 to June 2009. The full reports were retrieved for double-blind RCTs comparing paracetamol/NSAID combinations with 1 or both of their constituent drugs for pain relief. Variants of the search terms including "paracetamol/NSAIDs combination," "acetaminophen," "combination analgesics," "acute postoperative pain," and "ibuprofen/paracetamol" or individual drug names were entered as major subject headings. Reference lists of retrieved publications were checked for additional trials.

Exclusion criteria were (1) comparison of a paracetamol/NSAID combination with analgesics other than paracetamol or NSAIDs, (2) other pain models, e.g., chronic pain, and (3) retrospective, nonrandomized, or nonblinded trials. The retrieved reports were stratified according to the NSAID in the combination, the mode of administration (oral, IM, IV, rectal), and the surgical procedures studied.

Where possible, data on the following outcome measures were extracted from the retrieved publications in the form of mean/median and assessed for reported differences between the combination and constituent drug groups:

1. Pain intensity in the form of pain scores, e.g., postoperative visual analog scale (VAS) scores.
2. Supplemental postoperative analgesic requirements, e.g., opioid consumption.

In cases in which results of trials were reported only in graphical form, the means and SDs were estimated from these graphs. The difference in analgesic response among the study groups, i.e., % difference in pain intensity and % difference in analgesic supplementation, was extracted from the studies or calculated from the studies whenever possible. The mean/SD of the difference in analgesic response of all the positive studies was calculated.

Each study was graded for quality, using the validated scale of Jadad et al.,[6] on the extent to which its design, data collection, and statistical analysis minimized or avoided bias as follows:

1. Randomization: If the reports were described as randomized, 1 point was given. An additional point was given if the method of randomization was described and adequate (e.g., using computer-generated or table of random numbers). One point was deducted if the method of randomization was inappropriate (e.g., randomization according to age or birthdays).
2. Blinding: If the reports were described as double blind, 1 point was given. An additional point was given if the method of blinding was described and appropriate (e.g., use of double dummy). One point was deducted if the method of blinding was inappropriate.
3. Patients' withdrawals: If the reports described the numbers and reasons for withdrawals, 1 point was given.

The possible range for these scores in the included studies was 2 to 5. A Mann-Whitney *U* test was used to assess the relationships between the positive and negative trials and the quality scores. Subgroup analyses were performed for the combination versus paracetamol and combination versus NSAID by surgical model and by NSAID.

Statistical heterogeneity across the studies was evaluated both qualitatively and quantitatively using the funnel plot and Cochran *Q* test, respectively. The computer software package, SPSS for Windows (SPSS, Chicago, IL), and Comprehensive Meta-Analysis™ (Biostat, Englewood, NJ) were used.

## RESULTS

Thirty-two studies that evaluated paracetamol/NSAID combinations were found.[7–38] Eleven were excluded because of inadequate randomization, nonblinding, or comparison of the combinations with different classes of analgesics or studies in chronic pain.[7–17] Twenty-one RCTs in acute postoperative pain models with a total of 1909 patients were included for further analysis.[18–38]

Studies comparing paracetamol/NSAID combinations with paracetamol alone are summarized in Table 1, and those comparing paracetamol/NSAID combinations with NSAIDs alone are summarized in Table 2.

The evaluated NSAIDs were ibuprofen ($n$ = 6),[21,23,27,30,33,38] diclofenac ($n$ = 8),[19,20,26,29,31,32,34,36] ketoprofen ($n$ = 3),[18,22,25] ketorolac ($n$ = 1),[28] aspirin ($n$ = 1),[35] tenoxicam ($n$ = 1),[37] and rofecoxib ($n$ = 1).[24] The models studied were dental surgery ($n$ = 6)[20,23,24,27,29,30]; orthopedic surgery ($n$ = 5)[18,21,22,25,37]; gynecological/inguinal surgery ($n$ = 6)[19,31,32,34–36]; and ear, nose, and throat (ENT) surgery ($n$ = 4).[26,28,33,38] Of these, 13 compared the effect of the combination with both an NSAID and paracetamol[20–22,24–26,29,31,32,34,36–38]; 20 compared the combination with paracetamol alone[18–29,31–38] (Table 1); and 14 compared the combination with an NSAID alone (Table 2).[20–22,24–26,29–32,34,36–38]

### Results for Studies of a Combination Versus Paracetamol Alone

Twenty studies involving 1852 patients compared the efficacy of an analgesic combination with paracetamol alone (Table 1). Overall, 17 of these 20 studies (85%) showed that the combination was more effective than paracetamol alone in terms of lower pain scores, lower supplemental analgesic requirements, or better globally assessed pain relief (positive studies). For surgical model subgroup analysis, the ENT model had positive results for all 4 studies (100%)[26,28,33,38]; the dental model had 4 of 5 positive studies (80%)[20,23,24,27,29]; the orthopedic model had 4 of 5 positive studies (80%)[18,21,22,25,37]; and the gynecological/inguinal model had 5 of 6 positive studies (83%).[19,31,32,34–36] For NSAID subgroup analysis, all 5 ibuprofen studies showed consistently positive results (100%)[21,23,27,30,33,38]; the diclofenac studies had 6 of 8 positive results (75%)[19,20,26,29,31,32,34,36]; the 3 ketoprofen studies all showed positive results (100%)[18,22,25]; and the single rofecoxib, ketorolac, and aspirin studies each showed positive results.[24,28,35] However, the single tenoxicam combination study showed no difference in analgesic efficacy compared with paracetamol alone.[37]

Overall, mean (SD) reduction in pain intensity was 35.0% (10.9%); the reduction in analgesic supplementation was 38.8% (13.1%). The quality scores of the studies ranged from 2 to 5. The median quality score was 4 for the positive

**Table 1. Studies of Paracetamol/Nonsteroidal Antiinflammatory Drugs (NSAID) Combinations Versus Paracetamol Alone**

| Reference, quality score, study outcome | Sample size | Treatment groups | Type of surgery | Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures | Adverse events (significant difference between groups) |
|---|---|---|---|---|---|
| Aubrun et al.,[18] Score 3, +ve study | 50 | 1. Propacetamol 2000 mg<br>2. Ketoprofen 100 mg + propacetamol 2000 mg<br>Propacetamol 6 hourly, ketoprofen 8 hourly given for 24 h after surgery | Orthopedic surgery—spinal fusion surgery | 1. Pain intensity (VAS): +ve<br>2. Pain relief (VAS): −ve<br>3. Morphine usage (PCA): +ve<br>Pain intensity was 22% lesser<br>Morphine usage was 33% lesser | No difference<br>Nausea and vomiting: 28%–32%<br>Drowsiness: 48%–52% |
| Beck et al.,[19] Score 3, −ve study | 65 | 1. Paracetamol 20 mg/kg<br>2. Paracetamol 40 mg/kg<br>3. Diclofenac 100 mg + paracetamol 20 mg/kg<br>Single rectal dose with 24 h observation period after surgery | Gynecological surgery—vaginal or abdominal hysterectomy | 1. Pain scores (VAS): −ve<br>2. Morphine usage (PCA): −ve<br>No difference in the outcome measures | Nausea and vomiting: 13%–22%<br>Only morphine related adverse effects: more in group 1 which required more morphine |
| Breivik et al.,[20] Score 5, +ve study | 68 | 1. Diclofenac 100 mg<br>2. Paracetamol 1000 mg<br>3. Diclofenac 100 mg + paracetamol 1000 mg<br>Single rectal dose with 8 h observation period after surgery | Dental surgery—impacted third molar surgery | 1. Pain intensity (VAS): +ve<br>2. Pain relief score: +ve<br>3. Global assessment: +ve<br>Pain intensity was 41% lesser | No difference<br>Nausea and drowsiness: 25%–33% |
| Dahl et al.,[21] Score 5, +ve study | 61 | 1. Ibuprofen 800 mg<br>2. Paracetamol 1000 mg<br>3. Ibuprofen 800 mg + paracetamol 1000 mg<br>All drugs were given orally 1 h before surgery and again at 6 and 12 h after initial dose | Orthopedic surgery—anterior cruciate ligament reconstruction | 1. Pain scores (VAS): +ve<br>2. Supplemental analgesic requirements: +ve<br>Pain intensity was 35% lesser<br>Analgesic requirements was 68% lesser | No difference<br>Nausea and vomiting: 11% |
| Fletcher et al.,[22] Score 5, +ve study | 45 | 1. Propacetamol 2000 mg<br>2. Ketoprofen 50 mg<br>3. Ketoprofen 50 mg + propacetamol 2000 mg<br>4. Placebo<br>All drugs were given IV 6 hourly for 2 days after the surgery | Orthopedic surgery—disk surgery | 1. Pain intensity (VAS): +ve<br>2. Morphine usage (PCA): +ve<br>Pain intensity was 55% lesser<br>Morphine usage was 56% lesser | No difference<br>Nausea and vomiting: 14%–27%<br>Drowsiness: 7%–27%<br>Urinary retention: 14%–27% |
| Gazal et al.,[23] Score 5, +ve study | 201 | 1. Ibuprofen (5 mg/kg) + paracetamol (15 mg/kg)<br>2. Paracetamol (20 mg/kg)<br>3. Paracetamol (15 mg/kg)<br>Single oral dose given 1 h before the surgery | Dental surgery—extractions in children | 1. Pain intensity (children's hospital of eastern Ontario pain scale): +ve<br>2. 5 point face scale for distress: +ve<br>Pain intensity was 20% lesser | No adverse effects were reported |
| Haglund et al.,[24] Score 5, +ve study | 120 | 1. Rofecoxib 50 mg + paracetamol 1000 mg<br>2. Rofecoxib 50 mg<br>3. Paracetamol 1000 mg<br>4. Placebo<br>Single oral dose with 8 h observation period after surgery | Dental surgery—impacted third molar surgery | 1. Pain intensity (VAS): +ve<br>2. Global assessment for pain relief: +ve<br>3. % patients using rescue medication: +ve<br>Pain intensity was 20% lesser<br>% of patients using rescue medication was 31% lesser | No difference<br>Headache: 3%–12%<br>Drowsiness: 3%–10%<br>Fatigue: 11%–12% |
| Hiller et al.,[25] Score 5, +ve study | 120 | 1. Paracetamol 60 mg/kg rectally and 40 mg/kg orally<br>2. Ketoprofen 2 mg IV twice<br>3. Paracetamol + ketoprofen as above<br>One dose given after G.A. induction and second dose 8 h later | Orthopedic surgery—elective pediatric orthopedic procedures | 1. Objective Pain Scale (OPS): +ve<br>2. Morphine usage: +ve<br>3. Time to first morphine request: +ve<br>Pain intensity was 34% lesser<br>Morphine usage was 36% lesser<br>Time to first morphine was 54% longer | No difference<br>Nausea: 42%–56%<br>Vomiting: 47–63%<br>Urinary retention: 8% |
| Hiller et al.,[26] Score 3, +ve study | 71 | 1. Propacetamol 2 g<br>2. Diclofenac 75 mg<br>3. Propacetamol 2 g + diclofenac 75 mg<br>Single IV dose started after general anesthetic induction | ENT—tonsillectomy in adults | 1. Pain intensity (VAS): −ve<br>2. PCA oxycodone: +ve<br>No difference in pain intensity<br>PCA oxycodone was 29% lesser | No difference<br>Nausea: 33%–52%<br>Vomiting: 16%–32%<br>Headache: 24%–32% |

(*Continued*)

**Table 1. (*Continued*)**

| Reference, quality score, study outcome | Sample size | Treatment groups | Type of surgery | Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures | Adverse events (significant difference between groups) |
|---|---|---|---|---|---|
| Ianiro et al.,[27] Score 4, +ve study | 40 | 1. Paracetamol 1000 mg<br>2. Paracetamol 1000 mg + ibuprofen 600 mg<br>3. Placebo<br>Single oral dose 30 min before procedure | Dental surgery—dental root canal treatment | 1. Pain sensitivity from cold test or surgical drilling of tooth: +ve<br>No pain intensity or analgesic consumption outcomes used<br>Data cannot be used for statistical calculation | No adverse effects were reported |
| Mather et al.,[28] Score 2, +ve study | 80 | 1. Paracetamol 20 mg/kg<br>2. Placebo + morphine 0.1 mg/kg<br>3. Paracetamol 20 mg/kg + ketorolac 0.5 mg/kg<br>Single dose as premedication and 24 h after surgery. Paracetamol was given orally and ketorolac was given intramuscularly | ENT—tonsillectomy | Supplemental morphine usage: +ve<br>Supplemental morphine usage was 21% lesser | No difference between the paracetamol and combination group<br>Greater incidence of vomiting in morphine group, i.e., group 2<br>Vomiting: 15%–52% |
| Matthews et al.,[29] Score 4, −ve study | 28 | 1. Diclofenac 50 mg<br>2. Diclofenac 50 mg + paracetamol 500 mg<br>3. Paracetamol 500 mg<br>Single oral dose before surgery with 12 h observation period after surgery | Dental surgery—impacted third molar surgery | Pain intensity (VAS): −ve<br>No difference in the outcome measure | No adverse effects were reported |
| Montgomery et al.,[31] Score 4, +ve study | 59 | 1. Paracetamol 1500 mg<br>2. Diclofenac 100 mg<br>3. Paracetamol 1500 mg + diclofenac 100 mg<br>Single rectal dose given before surgery with 24 h observation after the surgery | Elective gynecological surgery | 1. Pain intensity (VAS): +ve<br>2. PCA morphine usage: +ve<br>Pain intensity was 40% lesser<br>Morphine usage was 38% lesser | Higher nausea and vomiting scores for group 1 because of more morphine usage<br>Nausea: 5%–13%<br>Vomiting: 26%–40% |
| Munishankar et al.,[32] Score 4, +ve study | 78 | 1. Paracetamol 1000 mg<br>2. Diclofenac 100 mg<br>3. Paracetamol 1000 mg + diclofenac 100 mg<br>First dose was given immediately after surgery. Paracetamol was given 6 hourly and diclofenac 8 hourly for 24 h after first dose | Gynecological surgery—cesarean section | 1. Pain intensity (VAS): −ve<br>2. PCA morphine: +ve<br>No difference in the pain intensity<br>Morphine usage was 38% lesser | No difference<br>Nausea and vomiting: 27%–42% |
| Pickering et al.,[33] Score 3, +ve study | 98 | 1. Paracetamol 20 mg/kg + rofecoxib 0.625 mg/kg<br>2. Paracetamol 20 mg/kg + ibuprofen 5 mg/kg<br>3. Paracetamol 20 mg/kg + placebo<br>All drugs were given orally 1 h before surgery. Then only paracetamol was given 4 hourly for 8 h after surgery | ENT—pediatric tonsillectomy | 1. Pain intensity (VAS)<br>2. Need for supplemental analgesic<br>+ve for paracetamol + ibuprofen group in VAS and analgesic requirements<br>−ve for paracetamol + rofecoxib group in VAS and analgesic requirements<br>Pain intensity was 33% lesser at time of administration of supplemental analgesia<br>% of patients using rescue medication was 34% lesser | No difference in vomiting or antiemetic use<br>Vomiting: 22%–33% |
| Riad et al.,[34] Score 5, +ve study | 108 | 1. Diclofenac 1 mg/kg<br>2. Paracetamol 40 mg/kg<br>3. Diclofenac 1 mg/kg + paracetamol 40 mg/kg<br>All drugs were given rectally 1 h before surgery | Inguinal hernia surgery in children | 1. Wong and Baker scale (FACES) Pain Rating Scale: +ve<br>2. Supplemental morphine requirements: +ve<br>Pain intensity was 33% lesser<br>Morphine usage was 47% lesser | Time to discharge from recovery room significantly longer for paracetamol group |

(*Continued*)

**Table 1. (*Continued*)**

| Reference, quality score, study outcome | Sample size | Treatment groups | Type of surgery | Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures | Adverse events (significant difference between groups) |
|---|---|---|---|---|---|
| Rubin et al.,[35] Score 4, +ve study | 246 | 1. Paracetamol 648 mg and acetylsalicylic acid 648 mg<br>2. Acetylsalicylic acid 800 mg and caffeine 65 mg<br>3. Paracetamol 1000 mg<br>4. Placebo single oral dose | Gynecological surgery—episiotomy | 1. Pain intensity (0–4 scale)-+ve<br>2. Remedication: −ve<br>Pain intensity was 50% lesser<br>No difference in the requirement for remedication | No difference<br>Nausea and drowsiness reported as 4%–9% |
| Siddik et al.,[36] Score 3, +ve study | 80 | 1. Placebo<br>2. Diclofenac 100 mg rectally<br>3. Propacetamol 2 g IV<br>4. Propacetamol 2 g + diclofenac 100 mg as above<br>Paracetamol was given IV 6 hourly and diclofenac rectally 8 hourly for 24 h after surgery | Gynecological surgery—caesarean section | 1. Pain intensity (VAS): +ve<br>2. PCA morphine: +ve<br>Pain intensity was 37% lesser<br>Morphine usage was 49% lesser | No difference<br>Nausea and vomiting: 10%–16%<br>Drowsiness: 5%<br>Purities: 20%–30% |
| Van Lancker et al.,[37] Score 3, −ve study | 74 | 1. Propacetamol 30 mg/kg<br>2. Tenoxicam 0.5 mg/kg<br>3. Propacetamol 30 mg/kg + tenoxicam 0.5 mg/kg<br>4. Placebo<br>All drugs were given IV 1 h before the surgery, then only proparacetamol was repeated after 6 h with observation period of 24 h after surgery | Orthopedic surgery—arthroscopy | 1. Pain intensity (VAS): −ve<br>No difference in pain intensity | No difference<br>Nausea and vomiting: 4%–8%<br>Headache: 4%–12%<br>Drowsiness: 4% |
| Viitanen et al.,[38] Score 4, +ve study | 160 | 1. Paracetamol 40 mg/kg<br>2. Ibuprofen 15 mg/kg<br>3. Paracetamol 40 mg/kg + ibuprofen 15 mg/kg<br>4. Placebo<br>Single rectal dose | ENT—pediatric tonsillectomy | Supplemental analgesic requirements during first 24 h and after discharge: +ve<br>Supplemental analgesic requirements was 25% lesser after discharge | Vomiting: 24%–32%<br>Drowsiness: 5%<br>Abdominal pain: 3%–10%<br>Paracetamol group was drowsier than other groups |
| Total | 1852 | | | | |

Study outcome: "+ve" means that the combination was superior to paracetamol alone. "−ve" means that the combination was not superior to paracetamol alone.
VAS = visual analog scale; PCA = patient-controlled analgesia; ENT = ear-nose-throat.

studies and 3 for the negative studies (Mann-Whitney *U* test: $P = 0.18$).

Figure 1 is a funnel plot of the included studies for the treatment effect against a measure of study size. The asymmetric funnel suggests the possibility of a systematic difference between smaller and larger studies or systematic heterogeneity. In addition, a test of statistical heterogeneity yielded a highly significant result ($Q$ value = 38.4, $df(Q) = 18$, $P = 0.003$), giving substantial evidence of statistical heterogeneity. The results of these heterogeneity tests further add legitimacy for the appropriateness of a qualitative over quantitative systematic review for these studies.

## Results for Studies of a Combination Versus NSAIDs Alone

Fourteen studies involving 1129 patients compared the efficacy of an analgesic combination with an NSAID alone (Table 2). Overall, 9 of these 14 studies (64%) showed that the combination was more effective than an NSAID alone in terms of lower pain scores, lower supplemental analgesic requirements, or better globally assessed pain relief for the combination group. For surgical model subgroup analysis, the ENT model showed positive results for both studies (100%)[26,38]; the dental model had 3 of 4 positive studies (75%)[20,24,29,30]; the orthopedic model had 2 of 4 positive studies (50%)[21,22,25,37]; and the gynecological model had 2 of 4 positive studies (50%).[31,32,34,36] For the NSAID subgroup analysis, the ibuprofen studies had 2 of 3 positive results (67%)[21,30,38]; the diclofenac studies had 4 of 7 positive results (57%)[20,26,29,31,32,34,36]; both the ketoprofen studies had positive results (100%)[22,25]; and the single rofecoxib combination study showed positive results.[24] However, the single tenoxicam combination study showed no difference in analgesic efficacy compared with an NSAID alone.[37]

Overall, the mean (SD) reduction in pain intensity was 37.7% (26.6%); the reduction in analgesic supplementation was 31.3% (13.4%). The quality scores for the studies ranged from 3 to 5. The median value for the positive studies was 5 and 4 for the negative studies (Mann-Whitney *U* test: $P = 0.39$).

Figure 2 is a funnel plot of the included studies for the treatment effect against a measure of study size. Once again, the asymmetric funnel suggests the presence of systematic heterogeneity. In addition, a test of statistical heterogeneity yielded a highly significant result ($Q$ value = 35.4, $df(Q) = 13$, $P = 0.002$), giving substantial evidence of statistical heterogeneity.

**Table 2. Studies of Paracetamol/Nonsteroidal Antiinflammatory drugs (NSAID) Combinations Versus NSAIDs Alone**

| Reference, quality score, study outcome | Sample size | Treatment groups | Type of surgery | Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures | Adverse events (significant difference) |
|---|---|---|---|---|---|
| Breivik et al.,[20] Score 5, +ve study | 68 | 1. Diclofenac 100 mg<br>2. Paracetamol 1000 mg<br>3. Diclofenac 100 mg + paracetamol 1000 mg<br>Single oral dose with 8 h observation period after surgery | Dental surgery—impacted third molar surgery | 1. Pain intensity (VAS): +ve<br>2. Pain relief score: +ve<br>3. Global assessment: +ve<br>Pain intensity was 50% lesser | No difference<br>Nausea and drowsiness: 25%–33% |
| Dahl et al.,[21] Score 5, −ve study | 61 | 1. Ibuprofen 800 mg<br>2. Paracetamol 1000 mg<br>3. Ibuprofen 800 mg + paracetamol 1000 mg<br>All drugs were given orally 1 h before surgery and again at 6 and 12 h after initial dose | Orthopedic surgery—anterior cruciate ligament reconstruction | 1. Pain scores (VAS): −ve<br>2. Supplemental analgesic requirements: −ve<br>No difference in the outcome measures | No difference<br>Nausea and vomiting: 11% |
| Fletcher et al.,[22] Score 5, +ve study | 45 | 1. Propacetamol 2000 mg<br>2. Ketoprofen 50 mg<br>3. Ketoprofen 50 mg + propacetamol 2000 mg<br>4. Placebo<br>All drugs were given IV 6 hourly for 2 days after the surgery | Orthopedic surgery—disk surgery | 1. Pain intensity (VAS): +ve<br>2. Morphine usage (PCA): +ve<br>Pain intensity was 40% lesser<br>Morphine usage was 56% lesser | No difference<br>Nausea and vomiting: 14%–27%<br>Drowsiness: 7%–27%<br>Urinary retention: 14%–27% |
| Haglund et al.,[24] Score 5, +ve study | 120 | 1. Rofecoxib 50 mg + paracetamol 1000 mg<br>2. Rofecoxib 50 mg<br>3. Paracetamol 1000 mg<br>4. Placebo<br>Single oral dose with 8 h observation period after surgery | Dental surgery—impacted third molar surgery | 1. Pain intensity (VAS): +ve<br>2. Global assessment for pain relief: +ve<br>3. % patients using rescue medication: +ve<br>Pain intensity was 13% lesser<br>% of patients using rescue medication was 23% lesser | No difference<br>Headache: 3%–12%<br>Drowsiness: 3%–10%<br>Fatigue: 11%–12% |
| Hiller et al.,[25] Score 5, +ve study | 120 | 1. Paracetamol 60 mg/kg rectally and 40 mg/kg orally<br>2. Ketoprofen 2 mg IV twice<br>3. Paracetamol + ketoprofen as above<br>One dose given after GA induction and second dose 8 h later | Orthopedic surgery—elective pediatric orthopedic procedures | 1. Objective Pain Scale (OPS): +ve<br>2. Morphine usage: +ve<br>3. Time to first morphine request: +ve<br>Pain intensity was 31% lesser<br>Morphine usage was 26% lesser<br>Time to first morphine was 33% longer | No difference<br>Nausea: 42%–56%<br>Vomiting: 47%–63%<br>Urinary retention: 8% |
| Hiller et al.,[26] Score 3, +ve study | 71 | 1. Propacetamol 2 g<br>2. Diclofenac 75 mg<br>3. Propacetamol 2 g + diclofenac 75 mg<br>All drugs were IV single dose | ENT—tonsillectomy in adults | 1. Pain intensity (VAS): −ve<br>2. PCA oxycodone: +ve<br>No difference in pain intensity<br>PCA oxycodone was 14% lesser | No difference<br>Nausea: 33%–52%<br>Vomiting: 16%–32%<br>Headache: 24%–32% |
| Matthews et al.,[29] Score 4, −ve study | 28 | 1. Diclofenac 50 mg<br>2. Diclofenac 50 mg + paracetamol 500 mg<br>3. Paracetamol 500 mg<br>Single oral dose before surgery | Dental surgery—impacted third molar surgery | Pain intensity (VAS): −ve<br>No difference in pain intensity | No adverse effects were reported |
| Menhinick et al.,[30] Score 4, +ve study | 57 | 1. Placebo<br>2. Ibuprofen 600 mg<br>3. Ibuprofen 600 mg + paracetamol 1000 mg<br>All drugs were administered after dental surgery<br>Single oral dose with 8 h observation period after surgery | Dental surgery—impacted third molar surgery | 1. Pain intensity (VAS) and categorical pain scale: +ve<br>2. Pain relief for 8 h postoperatively: +ve<br>Pain intensity was 82% lesser | No difference<br>Nausea: 5%–21%<br>Headache: 28%–53% |
| Montgomery et al.,[31] Score 4, −ve study | 59 | 1. Paracetamol 1500 mg<br>2. Diclofenac 100 mg<br>3. Paracetamol 1500 mg + diclofenac 100 mg<br>Single rectal dose given before surgery with 24 h observation after the surgery | Elective gynecological surgery | 1. Pain intensity (VAS): −ve<br>2. PCA morphine usage: −ve<br>No difference in the outcome measures | Nausea: 5%–13%<br>Vomiting: 26%–40%<br>Significantly higher nausea and vomiting scores for group 1 |

(*Continued*)

**Table 2. (*Continued*)**

| Reference, quality score, study outcome | Sample size | Treatment groups | Type of surgery | Outcome measures and analgesic results for combination/% difference in the improvement of outcome measures | Adverse events (significant difference) |
|---|---|---|---|---|---|
| Munishankar et al.,[32] Score 4, −ve study | 78 | 1. Paracetamol 1000 mg<br>2. Diclofenac 100 mg<br>3. Paracetamol 1000 mg + diclofenac 100 mg<br>Paracetamol was given 6 h and diclofenac 8 hourly for 24 h after first dose | Gynecological surgery—caesarean section | 1. Pain intensity (VAS): −ve<br>2. PCA morphine: −ve<br>No difference in the outcome measures | No difference<br>Nausea and vomiting: 27%–42% |
| Riad et al.,[34] Score 5, +ve study | 108 | 1. Diclofenac 1 mg/kg<br>2. Paracetamol 40 mg/kg<br>3. Diclofenac 1 mg/kg + paracetamol 40 mg/kg<br>All drugs were given rectally 1 h before surgery | Inguinal hernia surgery in children | 1. Wong and Baker scale (FACES) Pain Rating Scale: +ve<br>2. Supplemental morphine requirements: +ve<br>Morphine usage was 35% lesser | No adverse effects were reported<br>Time to discharge from recovery room significantly longer for paracetamol group |
| Siddik et al.,[36] Score 3, +ve study | 80 | 1. Placebo<br>2. Diclofenac 100 mg rectally<br>3. Propacetamol 2 g IV<br>4. Propacetamol 2 g + diclofenac 100 mg as above<br>Paracetamol given IV 6 h and diclofenac rectally 8 hourly for 24 h after surgery | Gynecological surgery—caesarean section | 1. Pain intensity (VAS): −ve<br>2. PCA morphine: +ve<br>No difference in the pain intensity<br>Morphine usage was 38% lesser | No difference<br>Nausea and vomiting: 10%–16%<br>Drowsiness: 5%<br>Purities: 20%–30% |
| Van Lancker et al.,[37] Score 3, −ve study | 74 | 1. Propacetamol 30 mg/ kg<br>2. Tenoxicam 0.5 mg/kg<br>3. Propacetamol 30 mg kg + tenoxicam 0.5 mg/kg<br>4. Placebo<br>All drugs were given IV 1 h before the surgery, then only proparacetamol was repeated after 6 h with observation period of 24 h after surgery | Orthopedic surgery—arthroscopy | 1. Pain intensity (VAS): −ve<br>No difference in pain intensity | No difference<br>Nausea and vomiting: 4%–8%<br>Headache: 4%–12%<br>Drowsiness: 4% |
| Viitanen et al.,[38] Score 4, +ve study | 160 | 1. Paracetamol 40 mg/kg<br>2. Ibuprofen 15 mg/kg<br>3. Paracetamol 40 mg/kg + ibuprofen 15 mg/kg<br>4. Placebo<br>Single rectal dose | Pediatric tonsillectomy | Supplemental analgesic requirements during first 24 h & after discharge: +ve<br>Supplemental analgesic requirements were 27% lesser after discharge | Vomiting: 24%–32%<br>Drowsiness: 5%<br>Abdominal pain: 3%–10%<br>Paracetamol group was drowsier than other groups |
| Total | 1129 | | | | |

Study outcome: "+ve" means that the combination was superior to NSAID alone. "−ve" means that the combination was not superior to NSAID alone.
VAS = visual analog scale; PCA = patient-controlled analgesia.

There was no evidence of an increased incidence of side effects with combinations compared with individual drugs alone. Most studies reported no difference between the side effect profiles with combination therapy versus single-drug therapy. The incidence of nausea and vomiting was significantly higher in some studies for the single-therapy groups that required more morphine as rescue medication.[19,31] In general, adverse effects were mild and infrequent in all the studies, and mostly related to known side effects of the investigated drugs. The most common side effects reported were nausea, vomiting, drowsiness, and headache (Tables 1 and 2). There were no serious adverse effects reported for any of the combination analgesics tested in combination or alone.

## DISCUSSION

This review suggests that combining paracetamol and an NSAID confers additional analgesic efficacy over either drug alone. The combination of paracetamol and an NSAID was more effective than paracetamol or an NSAID alone in 85% and 64% of the studies, respectively. The subgroup analysis by surgical model and NSAID type confirms our overall results and further strengthens our conclusion. This conclusion is consistent with many previous expert reviews that recommend the use of combination analgesics.[3,4,39–45] The recommendations from most of the previous expert reviews were based on logic rather than evidence, and in this review, we have attempted to provide the evidence.

Overall, ibuprofen was one of the NSAIDs most widely evaluated in the studies reviewed. The value of combining it with paracetamol was confirmed in all of the 5 studies against paracetamol alone,[21,23,27,30,33,38] and 2 of the 3 studies against an NSAID alone.[21,30,38] Ibuprofen has a well-established reputation for safety and efficacy compared with other NSAIDs.[46–54] However, even with ibuprofen, the risks are a function of the dose and duration of use.[55] Hence, the case for combining ibuprofen with paracetamol to obtain increased analgesia without increasing the dose of the NSAID is strong.

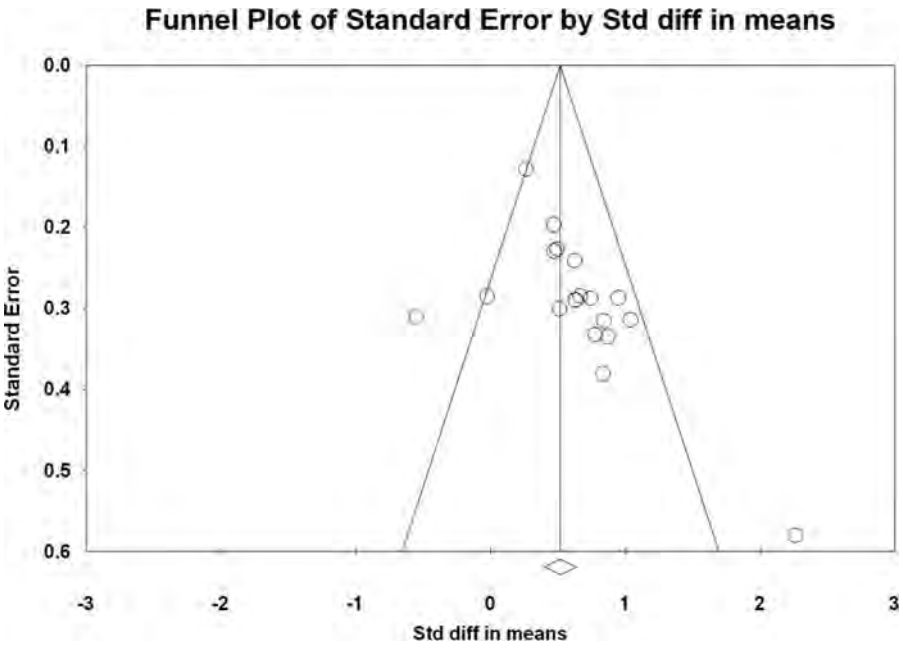


**Figure 1.** Funnel plot of the treatment effect against a measure of study size for studies of paracetamol/nonsteroidal antiinflammatory drug combinations versus paracetamol alone.

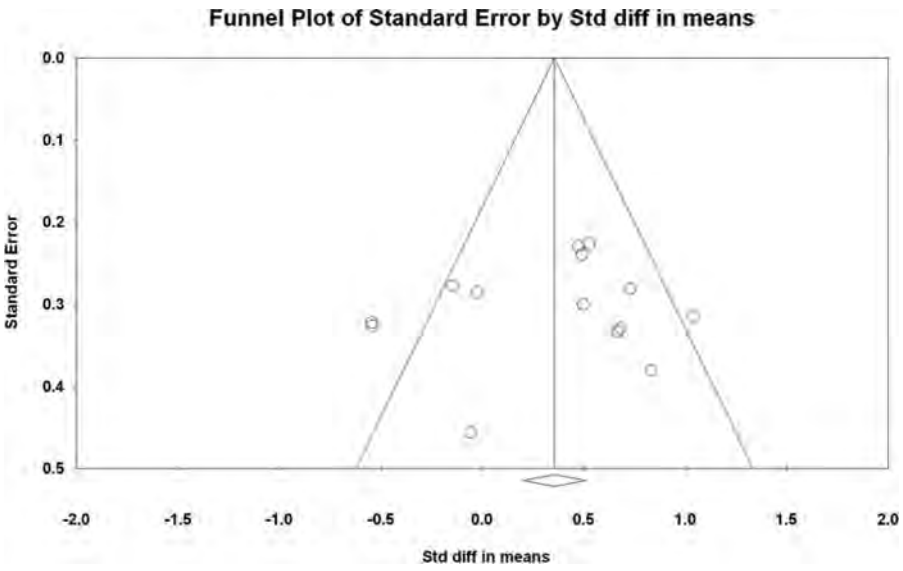


**Figure 2.** Funnel plot of the treatment effect against a measure of study size for studies of paracetamol/nonsteroidal antiinflammatory drug (NSAID) combinations versus NSAID alone.

Limitations of our study include its qualitative approach and the wide range of acute pain models included in the studies reviewed.[56] We note continuing debate over combining of different surgical models in acute pain studies.[56–59] A commentary criticized combining results from different surgical models in pain studies on the basis of comparisons of relative risk and seeking aid from the dubious ally of heterogeneity tests.[56] The authors argued that different models of acute pain may well produce different outcomes on the basis of the results for paracetamol 975/1000 mg in acute pain trials. On the contrary, there are at least 2 systematic reviews and 1 commentary that suggest that there is little difference between the different acute surgical models in the estimate of analgesic efficacy.[57–59] A quantitative meta-analysis would certainly not be possible for the included RCTs in this review because of heterogeneity of study design. Our subgroup analysis by surgical model provides considerable reassurance in relation to any influence of this heterogeneity on our overall qualitative findings.

Some of the negative studies included in this review may not have adequate sensitivity to detect a difference in pain scores between groups because the VAS pain scores were relatively low in the control groups. Moderately severe pain (e.g., VAS score >30 mm) is required in pain studies to achieve adequate sensitivity because it may not be possible to detect any difference if there is little or no pain.[60] The mean pain scores in the control groups were ≤30 mm in 4 of the 5 negative studies that compared the combination with NSAIDs.[21,29,31,32,37] In all 4 studies, the analgesics were given preemptively, either before surgery or immediately after surgery before pain developed.[21,29,31,37] In addition, it should be noted that some studies with small group sizes may not have adequate power to detect a difference even if present.[21,29,31,32,37]

Three recent animal studies also provide evidence in favor of combinations of paracetamol and NSAIDs for analgesia.[61–63] All 3 studies used the mouse acetic acid abdominal constriction test, a validated pain model in rodents, to measure analgesic effect of drug combinations.[64] Miranda et al.[61] compared antinociception induced by the intraperitoneal coadministration of combinations of paracetamol with the widely used NSAIDs diclofenac, ibuprofen, ketoprofen, meloxicam, metamizol, naproxen, nimesulide, parecoxib, and piroxicam. They concluded that all of the combinations were synergistic. Qiu et al.[62] and Miranda et al.[63] investigated the antinociceptive effect of oral paracetamol and ketoprofen alone or in combination and the antinociceptive effect of intraperitoneal administration of paracetamol, ketoprofen, and morphine alone or in combination, respectively. Similar dose-response curves were obtained in these 2 animal studies in favor of adding an NSAID to paracetamol.

There are some potential disadvantages in combining NSAIDs and paracetamol. A combination may be disadvantageous when individual drugs are specifically suited to a patient's symptoms (e.g., when only the antipyretic action of paracetamol is required for fever). Combining analgesics may increase the incidence of adverse effects. The use of fixed-dose combinations may reduce flexibility in dose titration, or conversely may expose patients to unnecessarily large doses of NSAIDs with consequent adverse effects, particularly in susceptible patients. Furthermore, combinations will not be suitable for patients with contraindications to either drug alone. For example, paracetamol should be used with caution (if at all) in patients with preexisting liver disease, whereas a history of gastrointestinal ulcers or renal impairment precludes use of traditional NSAIDs. The combination of paracetamol and long-acting NSAIDs such as tenoxicam has the theoretical disadvantage of pharmacokinetic incompatibility because tenoxicam has a much longer elimination half-life than paracetamol.

We conclude that a combination of acetaminophen and NSAIDs may provide superior analgesia than either drug alone. ■

## DISCLOSURE

Dr. Merry's unit has received grants from AFT Pharmaceuticals Ltd for research into a combination of paracetamol and ibuprofen.

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# Public Assessment Report

# Decentralised Procedure

## NUROMOL 200MG/500MG TABLETS

## (Ibuprofen /Paracetamol)

**UK/H/2853/001/DC**
**UK Licence No: PL 00063/0579**

**RECKITT BENCKISER HEALTHCARE (UK) LIMITED**

# LAY SUMMARY

On 15th September 2010, the UK granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation (licence) for the medicine Nuromol 200mg/500mg tablets.

Nuromol contains two active ingredients, ibuprofen and paracetamol.

Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs work by reducing pain, reducing swelling and lowering temperatures.

Paracetamol is an analgesic which works in a different way from ibuprofen to relieve pain and fever.

Nuromol 200mg/500mg tablets is used for the temporary relief of mild to moderate pain associated with:

- migraine
- headache
- backache
- period pain
- dental pain
- rheumatic and muscular pain
- pain of non-serious arthritis
- cold and flu symptoms
- sore throat and fever.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Nuromol 200mg/500mg tablets outweigh the risks; hence a Marketing Authorisation has been granted.

# TABLE OF CONTENTS

# Module 1

| | |
|---|---|
| **Product Name** | Nuromol 200mg/500mg tablets |
| **Type of Application** | Fixed combination, Article 10.b |
| **Active Substance** | Ibuprofen (200mg) and Paracetamol (500mg) |
| **Form** | Film-coated tablets |
| **Strength** | n/a |
| **MA Holder** | Reckitt Benckiser Healthcare (UK) Ltd<br>Slough, Berkshire<br>SL1 3UH<br>United Kingdom |
| **Reference Member State (RMS)** | UK |
| **CMS** | Poland |
| **Procedure Number** | UK/H/2853/001/DC |
| **End of Procedure** | Day 210 – 16th August 2010 |

# Module 2
# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT
Nuromol 200mg/500mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains ibuprofen 200 mg and paracetamol 500 mg.
For a full list of excipients see section 6.1

## 3 PHARMACEUTICAL FORM
Film-coated tablets (Tablets)
White to off-white, oval shaped, pearlescent tablets de-bossed with an identifying helix.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications
For the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. This product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

### 4.2 Posology and method of administration
For oral administration and short term-use only.
The lowest effective dose should be used for the shortest time necessary to relieve symptoms. The patient should consult a doctor if the symptoms persist or worsen or if the product is required for more than 3 days.

**Adults:** One tablet to be taken up to three times per day with water. Leave at least six hours between doses.
If the one tablet dose does not control symptoms, a maximum of two tablets may be taken up to three times a day. Leave at least six hours between doses.
Do not take more than six tablets (3000mg Paracetamol, 1200mg Ibuprofen) in any 24 hours period.
To minimise side effects, it is recommended that patients take Nuromol with food.

**Elderly**: No special dosage modifications are required (see section 4.4).
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.
Not for use by children under 18 years.

### 4.3 Contraindications
This product is contraindicated:
- In patients with a known hypersensitivity to ibuprofen, paracetamol or any other excipients.
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs (see Section 4.4).
- Patients with defects in coagulation.
- In patients with severe hepatic failure, severe renal failure or severe heart failure (see Section 4.4).
- In concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions (see Section 4.5).
- In concomitant use with other paracetamol-containing products – increased risk of serious adverse effects (see Section 4.5).
- During the last trimester of pregnancy due to risk of premature closure of the foetal ductus arteriosus with possible pulmonary hypertension (see Section 4.6)

**4.4 Special warnings and precautions for use**

The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2, and gastrointestinal and cardiovascular risks below) and by patients taking the dose with food (see Section 4.2).

*Elderly:*
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see Section 4.2).
Caution is required in patients with certain conditions:

- *Respiratory disorders:*

In patients suffering from, or with a history of, bronchial asthma or allergic disease NSAIDs have been reported to precipitate bronchospasm.

- *Cardiovascular, renal and hepatic impairment:*

The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see Section 4.3).

- *Cardiovascular and cerebrovascular effects*

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial data suggest that use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg daily) is associated with an increased risk of myocardial infarction.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

- *Gastrointestinal bleeding, ulceration and perforation:*

Gastrointestinal (GI) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see Section 4.5).
When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see Section 4.8).

- *SLE* and *mixed connective tissue disease:*

In patient with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis (see Section 4.8).

- *Dermatological:*

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

- *Impaired female fertility:*

The use of the product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

**4.5 Interaction with other medicinal products and other forms of interaction**

**This product** (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects (see Section 4.3).

**This product** (like any other ibuprofen containing products and NSAIDs) is contraindicated in combination with:

- Acetylsalicylic acid, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see Section 4.3).
- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see Section 4.3).

**This product** (like any other paracetamol containing products) should be used with caution in combination with:

- Chloramphenicol: Increased plasma concentration of chloramphenicol.
- Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.
- Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
- Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

**This product** (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:

- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, i.e. warfarin.
- Antihypertensives: NSAIDs may reduce the effects of these drugs.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see Section 4.4).
- Acetylsalicylic acid: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding the extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional use (see section 5.1)
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
- Ciclosporin: Increased risk of nephrotoxicity.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see Section 4.4).
- Diuretics: Reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs.
- Lithium: Decreased elimination of lithium.
- Methotrexate: Decreased elimination of methotrexate.
- Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

- Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
- Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- Zidovudine: Increased risk of haematological toxicity with NSAIDS are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

**4.6 Pregnancy and lactation**

*Pregnancy:*

There is no experience of use of this product in humans during pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known affects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child (see Section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

*Therefore if possible, the use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy (see Section 4.3).*

*Lactation:*

Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

*Therefore it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.*

See Section 4.4 regarding female fertility.

**4.7 Effects on ability to drive and use machines**

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected patients should not drive or operate machinery.

**4.8 Undesirable effects**

Clinical trials with this product have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

The following table lists adverse effects from pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short-term and long-term use.

| | | |
|---|---|---|
| **Blood and lymphatic system disorders** | Very rare (≤1/10,000) | Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia leucopenia, neutropenia, pancytopenia and thrombocytopenia).<br>**First signs are:** fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising and nose bleeding. |
| **Immune system disorders** | Very rare (≤1/10,000) | Hypersensitivity reactions have been reported. These may consist of non-specific allergic reactions and anaphylaxis.<br>Severe hypersensitivity reactions. **Symptoms can include:** facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). |
| **Psychiatric disorders** | Very rare (≤1/10,000) | Confusion, depression and hallucinations. |
| **Nervous system disorders** | Uncommon (≥1/1,000 to ≤1/100): | Headache and dizziness. |
| | Very rare (≤1/10,000) | Paraesthesia, optic neuritis and somnolence.<br>Single cases of aseptic meningitis in patients with existing autoimmune disorders (such as systemic lupus erythematosus and mixed connective tissue disease) during treatment with ibuprofen, with **symptoms such as:** stiff neck, headache, |

| | | |
|---|---|---|
| | | nausea, vomiting, fever or disorientation have been observed (see Section 4.4). |
| **Eye disorders** | Very rare (≤1/10,000) | Visual disturbance. |
| **Ear and labyrinth disorders** | Very rare (≤1/10,000) | Tinnitus and vertigo. |
| **Cardiac disorders** | Very rare (≤1/10,000) | Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.<br>Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (2400 mg daily), and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4). |
| **Respiratory and thoracic and mediastinal disorders** | Very rare (≤1/10,000) | Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea. |
| **Gastrointestinal Disorders** | Common (≥1/100 to ≤1/10) | Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting |
| | Uncommon (≥1/1,000 to ≤1/100): | Flatulence and constipation |
| | Uncommon (≥1/1,000 to ≤1/100): | Peptic ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemesis sometimes fatal, particularly in the elderly (see section 4.4).<br>Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn's disease following administration (see section 4.4). Less frequently gastritis has been observed and pancreatitis reported. |
| **Hepatobiliary disorders** | Very rare (≤1/10,000) | Abnormal liver function, hepatitis and jaundice.<br>In overdose paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury (see Section 4.9). |
| **Skin and subcutaneous tissue disorders** | Uncommon (≥1/1,000 to ≤1/100) | Rashes of various types including pruritis and urticaria.<br>Angioedema and swelling face. |
| | Very rare (≤1/10,000) | Hyperhiddrosis, purpura and photosensitivity.<br>Exfoliative dermatoses. Bullous reactions including erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. |
| **Renal and urinary disorders** | Very rare (≤1/10,000) | Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure. |
| **General disorders and administration site conditions** | Very rare (≤1/10,000) | Fatigue and malaise. |
| **Investigations** | Common (≥1/100 to ≤1/10) | Alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol.<br>Blood creatinine increased and blood urea increased. |
| | Uncommon (≥1/1,000 to ≤1/100) | Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine increased, haemoglobin decreased and platelet count increased. |

**4.9 Overdose**

**Paracetamol**

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

b) Regularly consumes alcohol in excess of recommended amounts.

c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

**Symptoms**
Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. 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.

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.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

**Ibuprofen**
**Symptoms**
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

**Management**
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties
**ATC Code:** M01AE51 – Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations.

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Paracetamol's exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX-2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

The clinical efficacy of ibuprofen and paracetamol has been demonstrated in pain associated with headache, toothache and dysmenorrhoea, and fever; furthermore efficacy has been shown in patients with pain and fever associated with cold and influenza and in pain models such as sore throat, muscular pain or soft tissue injury and backache.

This product is especially suitable for pain which requires stronger pain relief than ibuprofen 400 mg or paracetamol 1000 mg alone, and faster pain relief than ibuprofen.

**Summary of 2 tablet clinical data**

A randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain. The studies show that:

- This product provides more effective pain relief than paracetamol 1000 mg ($p<0.0001$) and ibuprofen 400 mg ($p< 0.05$) which are clinically and statistically significant.
- This product has a fast onset of action with 'confirmed perceptible pain relief' achieved in a median of 18.3 minutes. The onset of action was significantly more rapid than for ibuprofen 400 mg (23.8 minutes, $p=0.0015$). 'Meaningful pain relief' for this product was achieved in a median of 44.6 minutes, which was significantly faster than for ibuprofen 400 mg (70.5 minutes, $p<0.0001$)..
- Duration of analgesia was significantly longer for this product (9.1 hours) compared to paracetamol 500 mg (4 hours) or 1000 mg (5 hours).
- The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the product as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed significantly better than paracetamol 1000 mg ($p<0.0001$).
- A randomised, double-blind controlled clinical study was conducted with the product in the treatment of chronic knee pain. The study showed that:
- The product provides more effective pain relief than paracetamol 1000 mg in short-term treatment ($p<0.01$) and long term treatment ($p<0.01$).
- The global evaluation of the product by the subjects showed high levels of satisfaction with 60.2% rating the product as 'good' or 'excellent' as a long term treatment for a painful knee. The product performed significantly better than paracetamol 1000 mg ($p<0.001$).

## 5.2 Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty

stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours. In limited studies, ibuprofen appears in the breast milk in very low concentrations.

No significant differences in ibuprofen pharmacokinetic profile are observed in the elderly.
Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When this product was taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly.
The bioavailability and pharmacokinetic profiles of ibuprofen and paracetamol taken as this product are not altered when taken in combination as a single or repeat dose.

This product is formulated using a technology which releases both Ibuprofen and Paracetamol simultaneously, so that the active ingredients deliver a combination effect.

**5.3 Preclinical safety data**

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience. There are no new preclinical data of relevance to the prescriber which are additional to the data already presented in this Summary of Product Characteristics.

## 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Croscarmellose sodium
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate
Stearic acid

**Film Coat**
Polyvinyl alcohol
Titanium Dioxide
Talc
Macrogol
Potassium aluminium silicate (E555)
Polysorbate

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**
This medicinal product does not require any special storage conditions

**6.5 Nature and contents of container**
Opaque, white PVC with PVdC (polyvinylidene chloride), heat-sealed to aluminium foil, blister pack containing:
4, 6, 8, 10, 12, 16, 20, 24, 32 film-coated tablets
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**
No special requirements.

**7 MARKETING AUTHORISATION HOLDER**
Reckitt Benckiser Healthcare (UK) Ltd
Slough, Berkshire
SL1 3UH
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**
PL 00063/0579

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
15/09/2010

**10 DATE OF REVISION OF THE TEXT**
15/09/2010

# Module 3

# NUROMOL

## 200mg/500mg tablets
## Ibuprofen and Paracetamol

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to take it carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You **should not take the product for longer than 3 days.**
- If symptoms persist or worsen, consult your doctor
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

**In this leaflet:**



## 1. What Nuromol is and what it is used for

Your medicine is called Nuromol 200mg/500 mg tablets (called Nuromol throughout the rest of this leaflet).

Nuromol contains two active ingredients (which make the medicine work). **These are Ibuprofen and Paracetamol.**
Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs work by reducing pain, reducing swelling and lowering high temperatures.
Paracetamol is an analgesic which works in a different way from ibuprofen to relieve pain and fever.
Nuromol is used for the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever.

## 2. Before you take Nuromol

**Do not take Nuromol if you**

- are already taking **any other paracetamol containing product.**
- are taking any **other pain relieving products** including **ibuprofen, high dose aspirin** (above 75mg per day), or **other non-steroidal anti inflammatory drugs** (NSAIDs) including cyclo-oxygenase-2 (COX-2) specific inhibitors
- are **allergic to ibuprofen, paracetamol** or any other ingredients in Nuromol
- are **allergic to aspirin or other NSAID painkillers**
- have or ever had an **ulcer or bleeding in your stomach or duodenum** (small bowel)
- have **blood clotting (coagulation) disorder**
- suffer from **heart, liver or kidney failure**
- are in the **last 3 months of pregnancy**
- are **under 18** years old.

**Take special care and check with a doctor or pharmacist before taking Nuromol if you**

- are **elderly**
- have **asthma** or have suffered from asthma
- have **kidney, heart, liver or bowel** problems
- have **Systemic Lupus Erythematosus** (SLE) – a condition of the immune system affecting connective tissue resulting in joint pain, skin changes and disorder of other organs **or other mixed connective tissue disease**
- have **gastrointestinal disorders or chronic inflammatory bowel disease** (e.g. ulcerative colitis, Crohn's disease
- are in the **first 6 months of pregnancy** or are **breastfeeding**
- are **planning to become pregnant.**

If you have **heart problems**, previously **had a stroke** or think that you might be at risk of these conditions; (for example if you have **high blood pressure, diabetes or high cholesterol** or are a smoker), you should discuss your treatment with your doctor or pharmacist.

**Taking Nuromol with other medicines**
**Do not take Nuromol with**

- other **paracetamol containing** products
- other **NSAID containing products** such as aspirin, ibuprofen.

Special care is required as some medicines may interact with Nuromol, for example:

- **corticosteroid** tablets
- **antibiotics** (e.g. chloramphenicol or quinolones)
- **anti sickness** medicines (e.g. metoclopramide, domperidone)
- medicines to **thin the blood or prevent clotting** (e.g. warfarin)
- **heart stimulants** (e.g. glycosides)
- medicines for **high cholesterol** (e.g. cholestyramine)
- **diuretics** (to help you pass water)
- medicines for **high blood pressure**
- medicines to **suppress the immune system** (e.g. methotrexate, ciclosporine, tacrolimus)
- medicines for **mania or depression** (e.g. lithium or SSRIs)
- **mifepristone** (for pregnancy termination)
- **HIV medicines** (e.g. zidovudine).

**Always seek the advice of your doctor or pharmacist before you take Nuromol with other medicines.**

**Taking Nuromol with food**
To reduce the likelihood of side effects, take Nuromol with food.

Continued overleaf

**Pregnancy and breastfeeding**
Ask your doctor or pharmacist for advice before taking any medicine. Do not take if you are in the last 3 months of your pregnancy. Take special care if you are in the first 6 months of pregnancy.
Nuromol may make it more difficult to become pregnant. Ibuprofen belongs to a group of medicines which may impair fertility in women. This is reversible on stopping the medicine. You should inform your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

## 3. How to take Nuromol

For oral use and for short term use only.

Only use the minimum effective dose for the shortest time necessary to relieve your symptoms. **You should not take Nuromol for longer than 3 days.** If your symptoms worsen or persist, consult your doctor.

Take 1 tablet with **water and food**, up to 3 times a day.
Leave at least **6 hours between doses**.
If one tablet does not control symptoms, then a maximum of 2 tablets may be taken up to three times a day. **Do not take more than six tablets in any 24 hour period** (equivalent to 3000mg Paracetamol, 1200mg Ibuprofen a day).

**Not for use by children under 18 years.**

**If you take more Nuromol than you should**
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

**If you forget to take Nuromol**
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember it and then take the next dose at least 6 hours later.

## 4. Possible side effects

Like all medicines, Nuromol can cause side effects, although not everybody gets them.

**STOP TAKING the medicine and tell your doctor if you experience:**
- **heartburn, indigestion**
- **signs of intestinal bleeding** (severe stomach pain, vomiting blood or liquid with what looks like coffee granules, blood in the stools/motions, black tarry stools)
- **signs of inflammation of the brain lining** such as: stiff neck, headache, feeling or being sick, fever or feeling disorientated
- **signs of a severe allergic reaction** (swelling of the face, tongue or throat, difficult breathing, worsening of asthma).

**Other possible side effects**
**Common** (occurs in less than 1 in 10 people):
- stomach pain or discomfort, feeling or being sick, diarrhoea,
- higher levels of liver enzymes (shown in blood tests)

**Uncommon** (occurs in less than 1 in 100 people):
- headache and dizziness, wind and constipation, skin rashes, swelling of the face
- Reduction in red blood cells number or increase in platelets (blood clotting cells) number.

**Very rare** (occurs in less than 1 in 10,000 people):
- reduction in blood cells (causing sore throat, mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding, bruising and nosebleeds)
- visual disturbances, ringing in the ears, spinning sensation
- confusion, depression, hallucinations
- fatigue, generally feeling unwell
- severe skin reactions such as blistering
- high blood pressure, water retention
- liver problems (causing yellowing of the skin and white of eyes)
- kidney problems (causing increased or decreased urination, swelling of the legs)
- heart failure (causing breathlessness, swelling).

Medicines such as Nuromol may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. (See section 2)

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

## 5. How to store Nuromol

Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions.
Do not use Nuromol after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

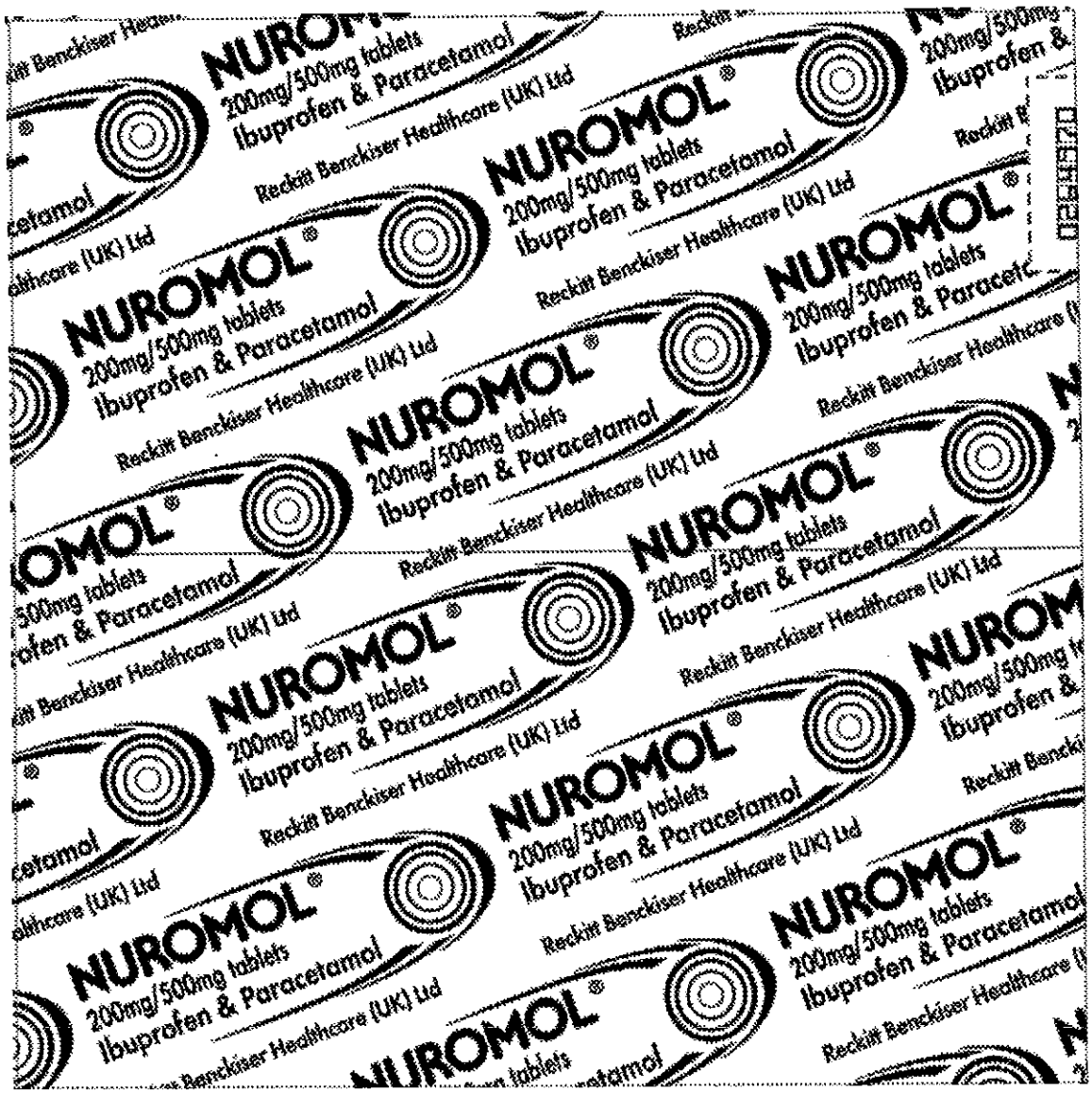
## 6. Further information

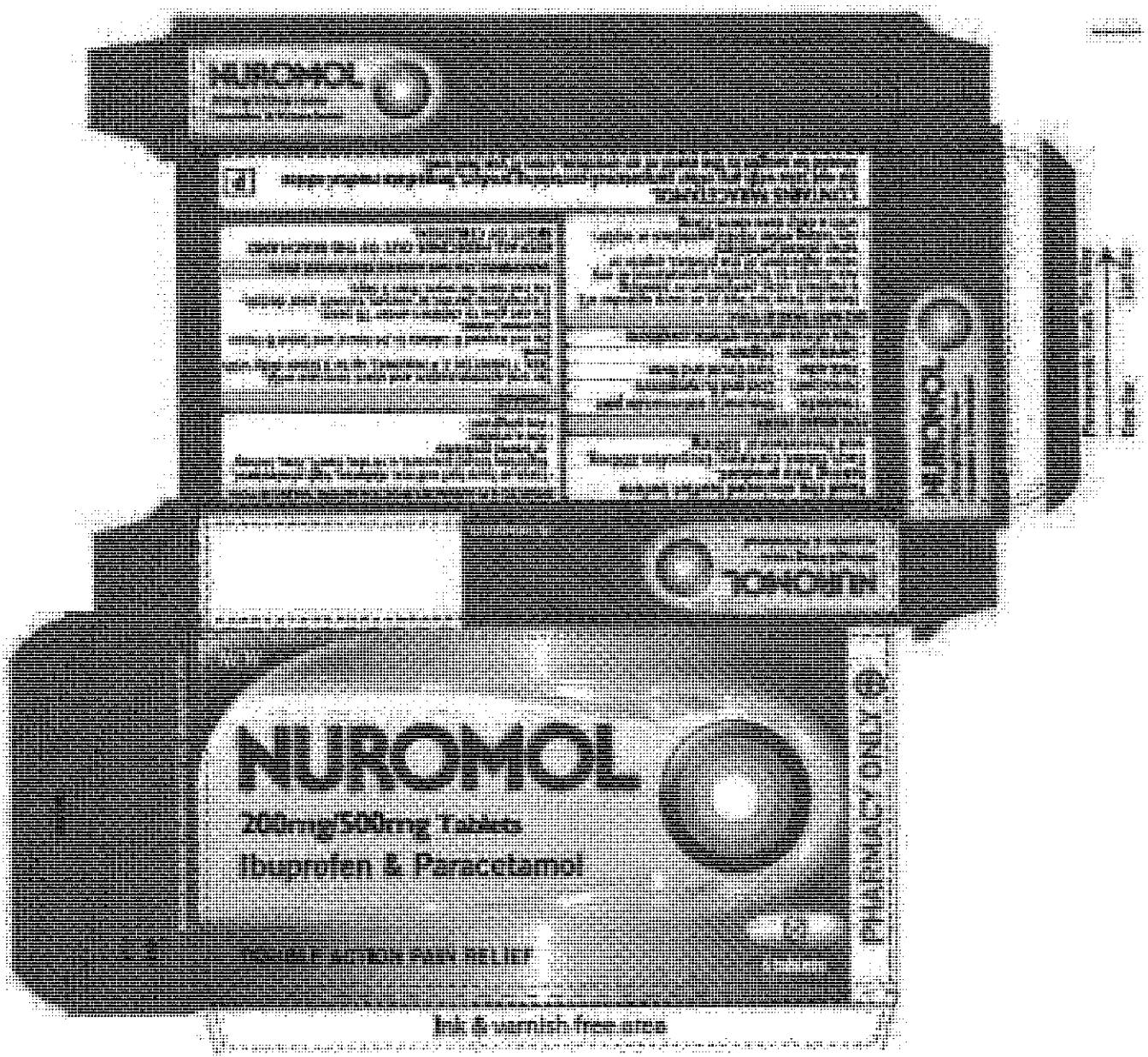
**What Nuromol contains**
- The active substances are ibuprofen and paracetamol. Each film-coated tablet contains 200 mg of ibuprofen and 500 mg of paracetamol
- The other ingredients are croscarmellose sodium, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, stearic acid. Film coating: polyvinyl alcohol, titanium dioxide, talc, macrogol, potassium aluminium silicate (E555), polysorbate

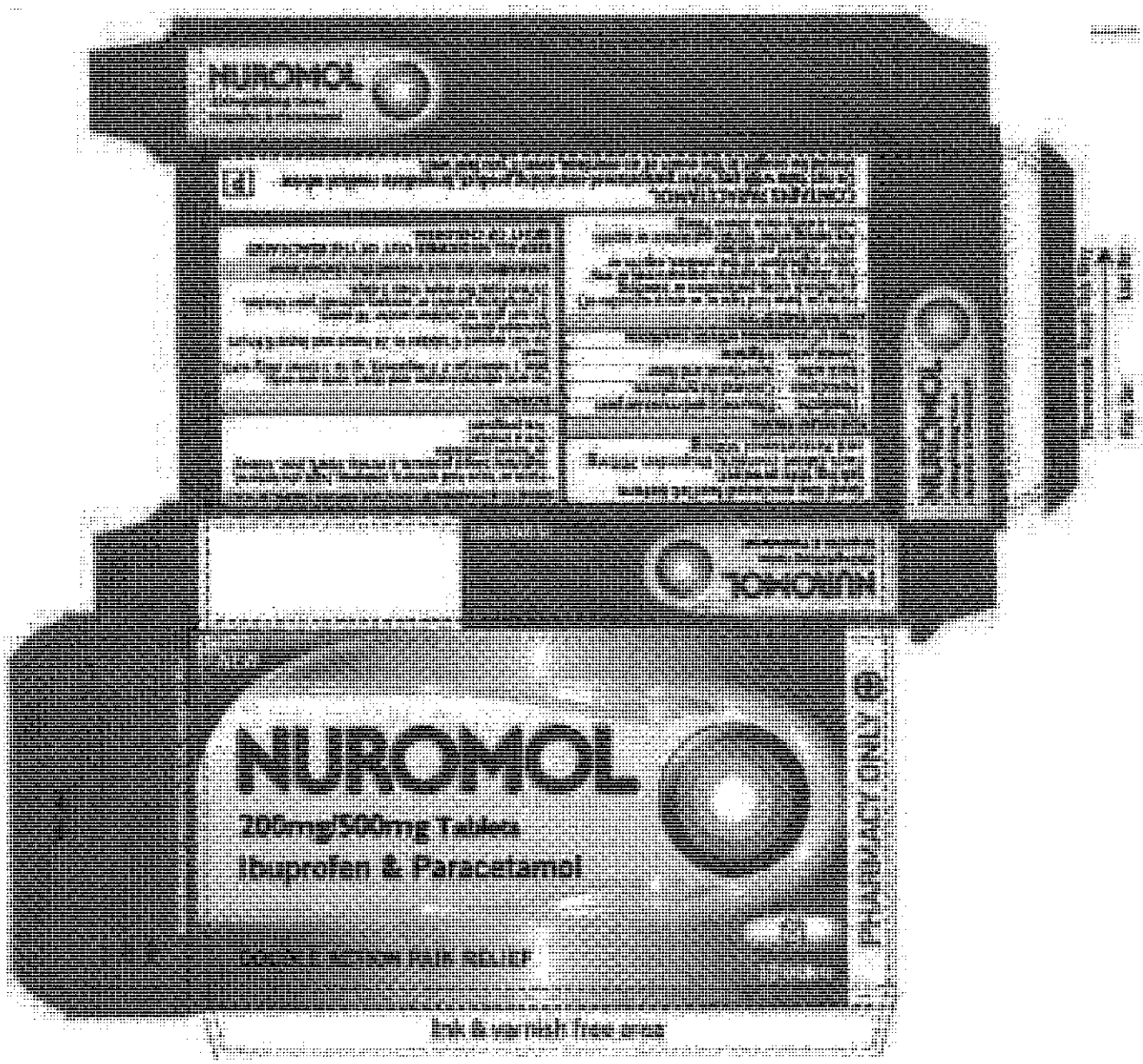
**What Nuromol looks like**
Nuromol tablets are white to off-white, oval shaped, film-coated pearlescent tablets marked with an identifying helix. They are available in blister packs containing 4, 6, 8, 10, 12, 16, 20, 24, 32 tablets. Not all pack sizes may be marketed.
Marketing authorisation holder and manufacturer
Licence holder : Reckitt Benckiser Healthcare (UK) Ltd, Slough, SL1 3UH, 0500 455 456
Manufactured by Reckitt Benckiser Healthcare International Ltd, Nottingham, NG90 2DB
This leaflet was last approved in 09/2010.

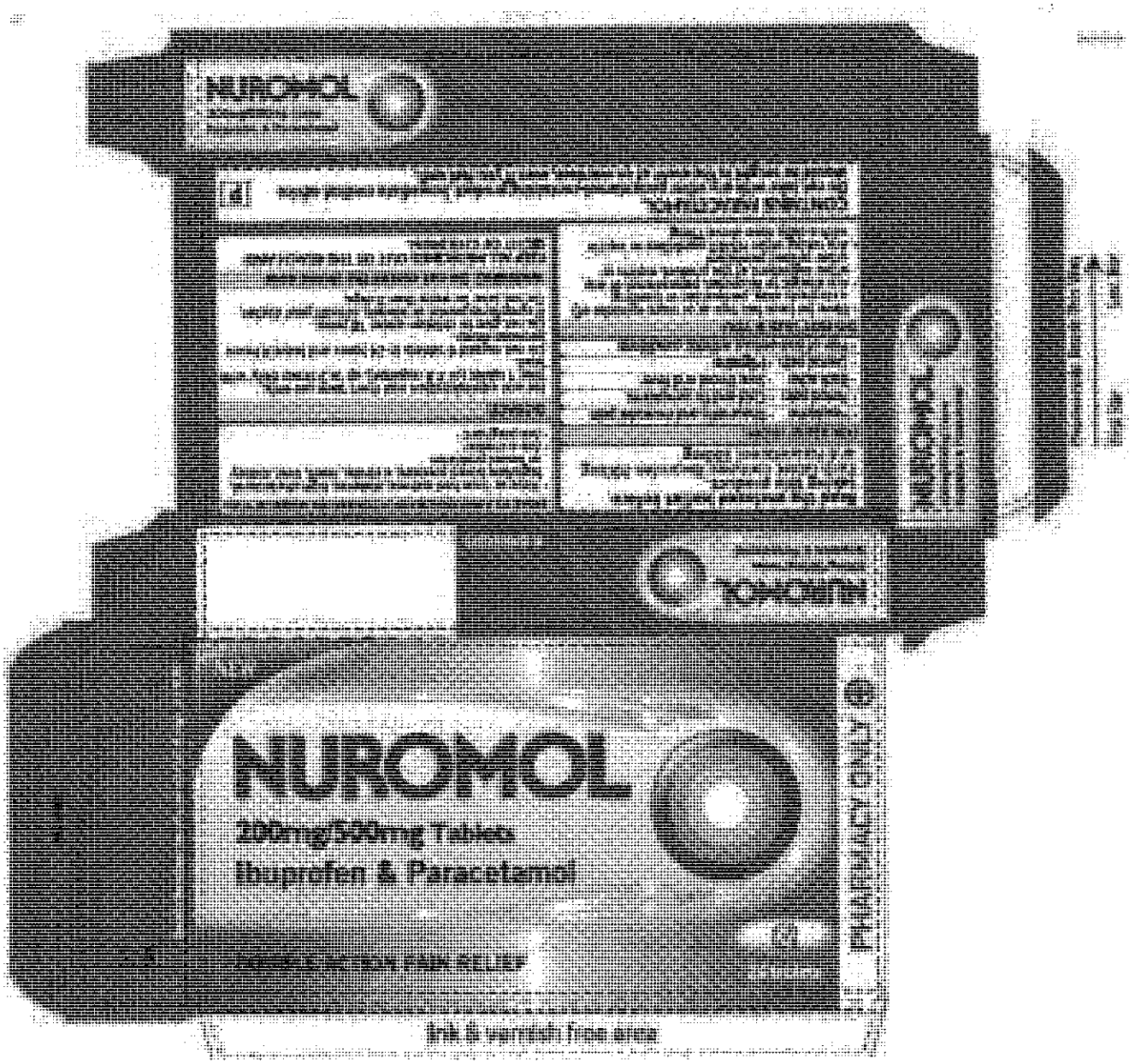
RBS2855

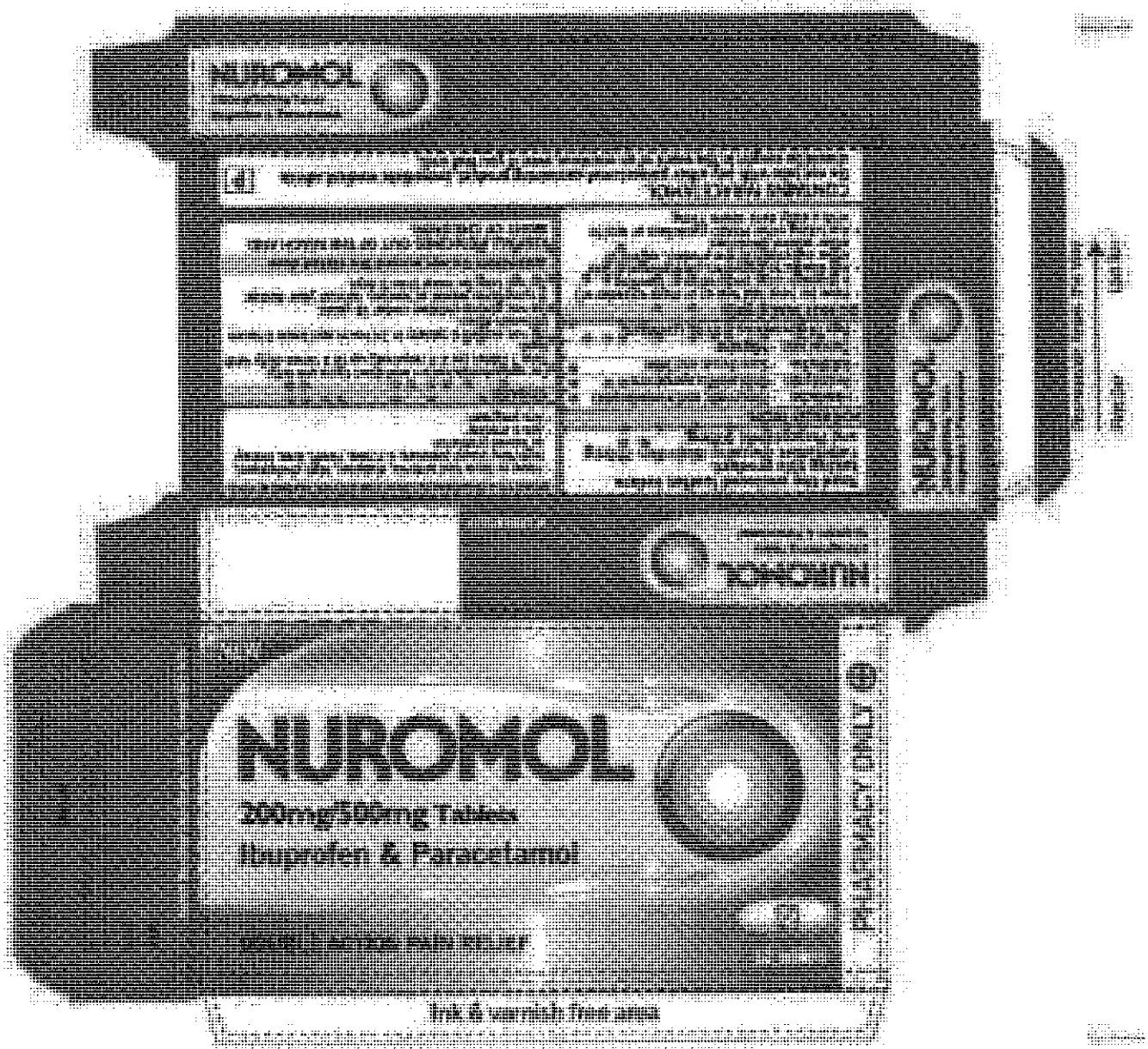
# Module 4
# Labelling




NUROMOL
NUROMOL
200mg/500mg Tablets
Ibuprofen & Paracetamol
Iris & varnish free area


NUROMOL
NUROMOL
200mg/500mg Tablets
Ibuprofen & Paracetamol
Ink & varnish free area


NUROMOL
NUROMOL
200mg/500mg Tablets
Ibuprofen & Paracetamol
Ink & varnish free area


NUROMOL
NUROMOL
200mg/500mg Tablets
Ibuprofen & Paracetamol
Ink & varnish free area

# Module 5
# Scientific discussion during initial procedure

## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Poland and the UK considered that the application for Nuromol 200mg/500mg tablets could be approved. The product is supplied by pharmacies and is indicated for the temporary relief of mild to moderate pain associated with:

- migraine
- headache
- backache
- period pain
- dental pain
- rheumatic and muscular pain
- pain of non-serious arthritis
- cold and flu symptoms
- sore throat and fever.

This application for Nuromol 200mg/500mg tablets is submitted as an abridged application according to Article 10.b of Directive 2001/83/EC, as a "fixed combination" containing 200mg ibuprofen and 500mg paracetamol.

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) which relieves pain and inflammation by the non-selective inhibition of prostaglandin biosynthesis at the site of tissue injury (peripherally). Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. At a maximum daily dose of ≤ 1.2 g ibuprofen predominately acts as an analgesic and antipyretic. Paracetamol is a weak inhibitor of cyclo-oxygenase (COX) 1 and 2 in peripheral tissues and has no significant anti-inflammatory activity. The analgesic and antipyretic properties of paracetamol are thought to be mediated centrally, although the mechanisms involved are not fully understood.

Ibuprofen and paracetamol are both widely available non-prescription compounds taken for the relief of pain and fever associated with well recognised and self-limiting illnesses. The efficacy and safety profile of ibuprofen and paracetamol are established and supported by extensive clinical data.

No new non-clinical studies were conducted, which is acceptable given that the product contains widely-used, well-known active substances.

To support this application, five clinical studies that investigate the efficacy and safety of Nuromol 200mg/500mg tablets were submitted:

• **Pharmacokinetic study NL0602**. An open-label, 4 way crossover, randomised, single centre study in healthy volunteers to assess bioavailability of a two tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in comparison to the single actives.

• **Pharmacokinetic study NL0603**. An open-label, randomised, repeat dose, two-way crossover study in healthy volunteers to examine the steady state pharmacokinetics of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' two or three times a day for 3 days.

• **Exploratory efficacy and tolerability study NL0408 in acute pain.** A double-blind, parallel-group, placebo-controlled randomised, single dose, two centre, modified factorial designed study to compare the analgesic efficacy and tolerability of the concomitant use of 1 or 2 ibuprofen 200 mg tablet(s) and paracetamol 500 mg tablet(s) with the single actives (2 x ibuprofen 200 mg and 2 x paracetamol 500 mg tablets) in the treatment of adults experiencing postoperative dental pain.

• **Pivotal efficacy and tolerability study NL0604 in acute pain**. A double-blind, parallel-group, placebo-controlled, randomised, single and multiple-dose phase, multicentre factorial design, two-part study examining the analgesic efficacy and tolerability of a 1 and 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', 1 x Ibuprofen 100 mg and Paracetamol 250 mg tablet, 1 or 2 ibuprofen 200 mg tablets, and 1 or 2 paracetamol 500 mg tablets in adults experiencing postoperative dental pain.

• **Pivotal efficacy and tolerability study NL0605 in chronic pain**. A randomised, double-blind, parallel group, multiple-dose 3-month study to examine the efficacy and tolerability of 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', 2 x 'Ibuprofen 200 mg and Paracetamol 500mg tablet', 2 x ibuprofen 200 mg caplets and 2 x paracetamol 500 mg caplets, all taken three times a day, in community patients with chronic knee pain.

For manufacturing sites within the Community, the RMS has accepted copies of current Manufacturer Authorisations issued by inspection services of the Competent Authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided an adequate Risk Management Plan (RMP) stating that all identified risks require routine risk minimisation measures only. No additional risk minimisation measures are required.

## II. ABOUT THE PRODUCT

| | |
|---|---|
| Name of the product in the Reference Member State | Nuromol 200mg/500mg tablets |
| Name(s) of the active substance(s) (INN) | Ibuprofen (200mg) and Paracetamol (500mg) |
| Pharmacotherapeutic classification (ATC code) | Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations (M01AE51) |
| Pharmaceutical form and strength(s) | 200mg/500mg Film-coated tablets |
| Reference numbers for the Decentralised Procedure | UK/H/2853/001/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Poland |
| Marketing Authorisation Number(s) | PL 00063/0579 |
| Name and address of the authorisation holder | Reckitt Benckiser Healthcare (UK) Ltd<br>Slough, Berkshire<br>SL1 3UH<br>United Kingdom |

# III SCIENTIFIC OVERVIEW AND DISCUSSION

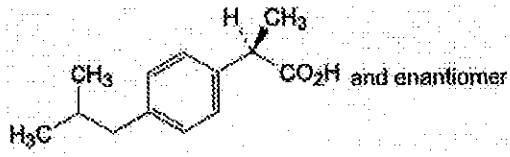
## III.1 QUALITY ASPECTS

### S. Active substance

**Ibuprofen**

INN/Ph.Eur name: Ibuprofen

Structural formula:




Molecular formula: $C_{13}H_{18}O_2$

Appearance: White odourless crystalline powder or colourless crystals

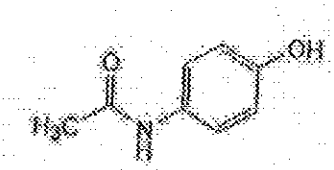
Molecular weight: 206.3

**Paracetamol**

INN/Ph.Eur name: Paracetamol

Chemical name: Acetaminophen
or N-Acetyl-p-aminophenol
or N-(4hydroxyphenyl)acetamide

Structural formula:




Molecular formula: $C_8H_9NO_2$

Appearance: white, free-flowing easily blendable powder.

Molecular weight: 151.2

Ibuprofen and paracetamol comply with their European Pharmacopoeia monographs.

All aspects of the manufacture of the active substances ibuprofen and paracetamol from their starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substances.

Appropriate specifications are provided for the active substances, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredients. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substances to be physically and chemically stable drugs, and supporting appropriate retest periods.

## P. Medicinal Product

### Other Ingredients

The other ingredients in the tablet are the pharmaceutical excipients croscarmellose sodium, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, stearic acid
The ingredients in the tablet film-coating are polyvinyl alcohol, titanium dioxide, talc, macrogol, potassium aluminium silicate (E555) and polysorbate.

All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin.
No genetically modified organisms (GMO) have been used in the preparation of this product.

### Pharmaceutical Development

The objective of the development programme was to produce a "fixed combination" product, which is a combination of 200mg of ibuprofen and 500mg of paracetamol.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution data was submitted for the product, pre and post encapsulation, demonstrating encapsulation had a negligible effect.

### Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The applicant has provided a commitment to submit process validation data for future commercial-scale batches of the finished product.

### Finished Product Specification

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

### Container-Closure System

The product is packaged in Opaque, white blister pack composed of polyvinyl chloride (PVC) and polyvinylidene chloride (PVdC), heat-sealed to aluminium foil.

The product is available in packs of 4, 6, 8, 10, 12, 16, 20, 24, 32 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years for an unopened sachet with no special storage conditions.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA forms**
The MAA form is pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.

## III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen and paracetamol are well known. As both paracetamol and ibuprofen are widely used, well-known active substances, and have been extensively co-administered and safely used in humans for a long period of time and the safety well documented, the applicant has not provided additional studies and further studies are not required.

The non-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

It is anticipated that this product will increase the amount of paracetamol and ibuprofen excreted into the environment as this product will 'cannibalise' the current sales of Nurofen and take market share away from that of other competing NSAID products. Therefore, in accordance with EMEA/CHMP/SWP/4447/00 - *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use*, the applicant has provided a satisfactory Phase I environmental risk assessment (ERA) report.

## III.3 CLINICAL ASPECTS

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. To support the application, five clinical studies that investigate the efficacy and safety of Nuromol 200mg/500mg tablets were submitted.

## CLINICAL PHARMACOLOGY

### Pharmacokinetics

The clinical pharmacokinetic programme was designed to investigate the single dose pharmacokinetic parameters of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in comparison to ibuprofen and paracetamol single actives and to confirm that there was no pharmacokinetic drug-drug interaction. In addition, study NL0603 was performed to investigate the steady state pharmacokinetics of the fixed combination product, to confirm that there was no drug accumulation, and to support the dosing interval of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

### Study NL0602

An open-label, 4 way crossover, randomised, single centre study in healthy volunteers to assess bioavailability of a two tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in comparison to the single actives. The secondary objective was to examine the effects of food on the single dose pharmacokinetic profiles of the fixed combination of ibuprofen and paracetamol.

27 healthy volunteers (16 male and 11 female, aged 18 - 57 years) received a single dose of:
Treatment A: 2 x ibuprofen 200 mg tablets
Treatment B: 2 x paracetamol 500 mg tablets
Treatment C: 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in the fasted state
Treatment D: 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in the fed state

The study medication was given in random order on four separate occasions with a 3-7 day washout period between each medication.

The wash out period represents over 18 plasma half lives of ibuprofen and paracetamol providing ample opportunity for the subjects to recover. Prior to receiving the study medication the subjects fasted overnight, at the clinic, for approximately 10 hours and the randomised treatment was given the following day. For the fed treatment subjects ate a standard high-fat breakfast 30 minutes prior to administration of 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'.

Blood samples were taken for analysis of ibuprofen and paracetamol concentrations before dosing, and at 5, 10, 20, 30 and 40 minutes and 1, 1.25, 1.5, 2, 3, 6, 9, and 12 hours post dose. The primary variables derived from plasma ibuprofen and paracetamol concentrations for each treatment were $C_{max}$, $AUC_{0-t}$, $AUC_{0-inf}$, $t_{max}$, and $t_{1/2}$, and Kel.

Pharmacokinetic data from 25 subjects was included in the analysis. One subject withdrew consent after receiving two doses and another subject was withdrawn because of incorrect dosing. These data were excluded from the analysis as they were incomplete.

Following logarithmic transformation $C_{max}$, $AUC_{0-t}$ and $AUC_{0-inf}$ values were subjected to an analysis of variance (ANOVA), including terms for sequence, subject nested within sequence, period and treatment. The validity of all analyses was assessed by inspection of residual plots and the Shapiro-Wilks test for normality. Contrasts between each pair of treatments (least

square means) were performed with 90% confidence intervals (CI) for the difference between treatments constructed using residual mean square error obtained from ANOVA. The point and interval estimates were back transformed to give estimates of the ratio of the geometric least squares means and the corresponding 90% CIs. $t_{max}$ was analysed between each pair of treatments using a paired t-test. Additionally, 95% non-parametric confidence interval was constructed for the median difference in $t_{max}$ values based on the Hodges-Lehmann estimates.

All 27 subjects who were enrolled, randomised and dosed were included in the safety data review, along with the vital signs and changes in laboratory values.

The results for each active were as follows:

**Ibuprofen (fasted)**

**Table 3 Comparison of the ibuprofen single dose pharmacokinetic parameters of ibuprofen 200 mg tablet (Treatment A) and 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (Treatment C) (fasted)**

| | 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (Treatment C) | 2 x Ibuprofen 200 mg tablet (Treatment A) | Ratio (%) | 90% CI |
|---|---|---|---|---|
| $C_{max}$ (µg.mL)[a] | 31.46 | 30.16 | 104.29 | 95.80 – 113.41 |
| $AUC_{0-t}$ (µg/mL/h)[a] | 116.51 | 108.80 | 107.08 | 103.20 – 111.11 |
| $AUC_{0-inf}$ (µg/mL/h)[a] | 118.82 | 111.08 | 106.99 | 103.26 – 110.85 |
| | | | Median Difference | 95% CI for difference |
| $t_{max}$ (min)[b] | 75 | 75 | 7.5 (p = 0.4870)[c] | -15.0 – 37.5 |

[a] Geometric LS Mean; [b] Median; [c] Wilcoxon Matched Pairs Test

**Paracetamol (fasted):**

**Table 4 Comparison of the paracetamol single dose pharmacokinetic parameters for paracetamol tablet (Treatment B) and 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (Treatment C) (fasted)**

| | 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (Treatment C) | 2 x Paracetamol 500 mg tablet (Treatment B) | Ratio (%) | 90% CI |
|---|---|---|---|---|
| $C_{max}$ (µg.mL)[a] | 17.58 | 16.88 | 104.14 | 91.32 – 118.76 |
| $AUC_{0-t}$ (µg/mL/h)[a] | 50.27 | 48.29 | 104.10 | 100.08 – 108.29 |
| $AUC_{0-inf}$ (µg/mL/h)[a] | 52.95 | 50.62 | 104.60 | 100.56 – 108.82 |
| | | | Median Difference | 95% CI for difference |
| $t_{max}$ (min)[b] | 30 | 40 | -15.0 (p = 0.0386)[c] | -30.0 – 0.0 |

[a] Geometric LS Mean; [b] Median; [c] Wilcoxon Matched Pairs Test

**Fed versus Fasted : Combination tablet**

**Table 5 Comparison of the pharmacokinetic parameters for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (fed: fasted)**

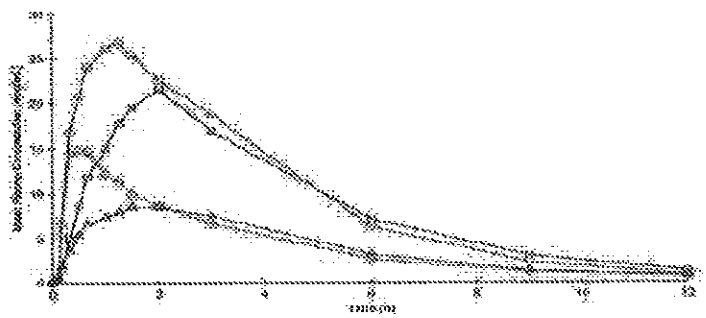
| | Ibuprofen Fed (Treatment D) | Ibuprofen Fasted (Treatment C) | Ratio (%) | 90% CI |
|---|---|---|---|---|
| $C_{max}$ (µg.mL)[a] | 24.03 | 31.46 | 76.38 | 70.25 – 83.06 |
| $AUC_{0-t}$ (µg/mL/h)[a] | 101.82 | 116.51 | 87.22 | 84.06 – 90.49 |
| $AUC_{0-inf}$ (µg/mL/h)[a] | 106.04 | 118.82 | 89.25 | 86.14 – 92.48 |
| | | | Median Difference | 95% CI for difference |
| $t_{max}$ (min)[b] | 120 | 75 | 25.0 (p = 0.0793)[c] | 0.0 – 45.0 |

| | Paracetamol Fed (Treatment D) | Paracetamol Fasted (Treatment C) | Ratio (%) | 90% CI |
|---|---|---|---|---|
| $C_{max}$ (µg.mL)[a] | 10.71 | 17.58 | 60.92 | 53.43 – 69.46 |
| $AUC_{0-t}$ (µg/mL/h)[a] | 45.69 | 50.27 | 90.89 | 87.38 – 94.54 |
| $AUC_{0-inf}$ (µg/mL/h)[a] | 48.72 | 52.85 | 92.01 | 88.45 – 95.71 |
| | | | Median Difference | 95% CI for difference |
| $t_{max}$ (min)[c] | 90 | 30 | 55.0 (p=0.0003)[c] | 30.0 – 90.0 |

[a] Geometric LS Mean; [b] Median; [c] Wilcoxon Matched Pairs Test

The rate of absorption of ibuprofen and paracetamol from 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is delayed following administration after food. The applicant concludes that the overall extent of absorption, as measured by area under the plasma concentration curve, for ibuprofen and paracetamol is bioequivalent for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in the fed and fasted state.

**Figure 3 Mean ibuprofen and paracetamol plasma concentration curves for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' – fed (Treatment D) and fasted (Treatment C)**



Key: ◇ Ibuprofen C; ○ Ibuprofen D; △ Paracetamol C; ▲ Paracetamol D

The extent of absorption is clearly not equivalent, as evidenced by the lower $C_{max}$ for both actives achieved in the fed state compared with the fasted. The curves in the graph above are obviously quite different. However, it is agreed that the preparations are bioequivalent in the fasted state. The effect of food is reflected with an appropriate warning in the SPC to the effect that this tablet should be taken with due regard to meals.

The study confirmed:

- The lack of pharmacokinetic drug-drug interaction between ibuprofen and paracetamol
- Confirmed the effects of food on the pharmacokinetic profiles of ibuprofen and paracetamol.

**Study NL0603**
An open-label, randomised, repeat dose, two-way crossover study in healthy volunteers to examine the steady state pharmacokinetics of a 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' two or three times a day for 3 days to support the posology.

26 healthy adult subjects (17 male and 9 female, aged 20-59 years) were randomised to receive repeat doses of 2 x 'Ibuprofen 200mg and Paracetamol 500mg tablet'
Treatment A: Twice a day (administered at 07.00 and 19.00)
Treatment B: Three times a day (administered at 07.00, 15.00 and 23.00)

Both treatments were taken on two separate occasions with a 3 to 7 day washout period between each three day treatment period. The washout period represents over 18 plasma half lives providing ample opportunity for the subjects to recover. Subjects remained in the clinic overnight for 4 nights and were provided with 2L of non-carbonated water to drink each day. Water was restricted for an hour before and for 2 hours after each dose except for the water provided with each dose. Subjects were provided with their meals at approximately the same times for both dosing regimes; breakfast at 09.00, lunch at 12.00, dinner at 17.00 and a snack at 21.00. Subjects were allowed to leave the unit on Day 5.

Prior to the first dose subjects fasted overnight, at the clinic, for approximately 10 hours and took the randomised treatment the following day (Day 2) and blood samples were taken before dosing, and at 10, 20, 40 and 60 minutes and 1.5, 2, 3, 6, 8, and 12 hours post dose for pharmacokinetic analysis on Days 2 and 4. In addition further samples were collected for twice daily regimen before administration of both doses on Day 3 and at 13, 14, 16, 20 and 24 hours post-dose 1 on Day 4. Whereas for three times a day regimen additional samples were collected before administration of dose 3 on Day 2, before administration of the three doses on Day 3 and at 16, 17, 18, 20 and 24 hours post-dose 1 on Day 4. Samples taken at 12 hours for twice daily regimen and 8 and 16 hours for three times a day regimen were trough samples.

The primary pharmacokinetic variables for each dosing regimen were area under the plasma concentration curve: AUC0-t (at the last measurable concentration), $AUC_{0\text{-}inf}$, $AUC_{tau}$ (for a dosing level); plasma concentration: $C_{max}$ (maximum), $C_{min}$ (minimum), $C_{av}$ (average), fluctuation ($[C_{max}-C_{min}]/C_{av}$) and swing ($[C_{max}-C_{min}]/C_{min}$) and $t_{max}$ for ibuprofen and paracetamol.

Logarithmically transformed trough values on Days 2, 3 and 4 were used to determine whether steady state had been reached for both treatments. The point estimates were then back-transformed to give estimates of the ratios of the geometric means and the corresponding 95% CI. Paired t-tests were also used for each treatment.

Following logarithmic transformation $C_{max}$ and $AUC_{0\text{-}t}$ values on Day 4 were subjected to an analysis of variance (ANOVA) including terms for sequence, subject nested within sequence, period and treatment. For comparison, point estimates and 90% CI for the difference between treatments were constructed using the residual mean square error obtained from the ANOVA. The point and interval estimates were then back-transformed to give estimates of the ratios of the geometric least squares means and the corresponding 90% CI.

Additionally, logarithmic AUCtau on Day 4 and AUC0-inf on Day 2 were subjected to an ANOVA (by treatment), including terms for sequence, subject nested within sequence and day. For comparison, point estimates and 90% CI for the difference between Day 4 and Day 2 were constructed using the residual mean square error obtained form the ANOVA, for each

treatment. The point and interval estimates were then back-transformed to give estimates of the ratios of the geometric least square means and the corresponding 90% CI.

Pharmacokinetic data from all 26 subjects were included in the analysis.

Analysis of minimum plasma concentration ($C_{min}$ or trough) data for ibuprofen and paracetamol at the same time of day did not reflect any significant differences for ibuprofen (**Table 9**). However, there was an apparent difference between paracetamol values on Day 2 and Day 3. There was no statistically significant difference between Day 3 and Day 4 paracetamol values, confirming that steady state had been achieved.

**Table 9: Comparison of ibuprofen and paracetamol $C_{min}$ data obtained at the same time of day for twice and three times a day dose regimen**

| Regimen | Day/ Sampling Time Comparison | LS Geometric Mean Ratio | 95% CI for Ratio | p- value |
|---|---|---|---|---|
| **Ibuprofen** | | | | |
| Twice a day (Treatment A) | D3, 12h vs. D2, 12h | 0.988 | 0.813 – 1.196 | 0.8847 |
| | D4, 0h vs. D3, 0h | 0.983 | 0.810 – 1.192 | 0.8584 |
| Three times a day (Treatment B) | D3, 8h vs. D2, 8h | 0.903 | 0.774 – 1.053 | 0.1915 |
| | D3, 16h vs. D2, 16h | 0.995 | 0.855 – 1.159 | 0.9647 |
| | D4, 0h vs. D3, 0h | 1.032 | 0.886 – 1.203 | 0.6883 |
| **Paracetamol** | | | | |
| Twice a day (Treatment A) | D3, 12h vs. D2, 12h | 1.343 | 1.216 – 1.484 | <0.0001 |
| | D4, 0h vs. D3, 0h | 0.951 | 0.861 – 1.050 | 0.3154 |
| Three times a day (Treatment B) | D3, 8h vs. D2, 8h | 1.365 | 1.252 – 1.487 | <0.0001 |
| | D3, 16h vs. D2, 16h | 1.043 | 0.958 – 1.135 | 0.3323 |
| | D4, 0h vs. D3, 0h | 0.887 | 0.795 – 0.845 | 0.0013 |

The mean plasma concentration ($AUC_{0\text{-}tau}$) on Day 4 for ibuprofen and paracetamol after twice and three times a day dosing were comparable to the first dose on Day 2, ($AUC_{0\text{-}inf}$). The least square geometric mean ratios and the associated 90% CI fall within the range of 80 – 110%. In addition, the mean peak plasma concentrations ($C_{max}$) after single and repeat dosing of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' are also comparable.

**Table 11: Comparison of the ibuprofen and paracetamol pharmacokinetic parameters after twice and three times a day dosing**

| Treatment Regimen | Day 4, $AUC_{tau}$ | Day 2, $AUC_{0\text{-}inf}$ | Ratio (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | LS Geometric Mean | | | |
| **Ibuprofen** | | | | |
| Twice a day (Treatment A) | 115.85 | 128.33 | 90.28 | 86.44 – 94.29 |
| Three times a day (Treatment B) | 112.30 | 129.82 | 86.50 | 83.15 – 89.99 |
| **Paracetamol** | | | | |
| Twice a day (Treatment A) | 50.20 | 47.54 | 105.60 | 101.92 – 109.40 |
| Three times a day (Treatment B) | 49.48 | 50.60 | 97.79 | 93.35 – 102.43 |

The $C_{max}$ and $t_{max}$ values for both ibuprofen and paracetamol were similar for both treatment regimens. $C_{min}$ values for both ibuprofen and paracetamol were higher following the three a day dosing regimen (Treatment B) compared to twice a day (Treatment A). There was therefore less fluctuation and swing with ibuprofen and paracetamol plasma concentrations following three times a day dosing compared to twice a day dosing. $AUC_{0\text{-}t}$ values for ibuprofen and paracetamol were higher following three times a day dosing compared to twice a day dosing, however $AUC_{tau}$ were similar for both dosing regimens. The three times a day

dosing regimen of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' provided more consistent therapeutic plasma concentrations of ibuprofen and paracetamol compared to twice daily dosing without the risk of accumulation.

| | $C_{max}$ (µg/mL) | $C_{min}$ (µg/mL) | $C_{av}$ (µg/mL) | Fluctuation | Swing | $AUC_{0-t}$ (µg/mL.h) | $AUC_{tau}$ (µg/mL.h) | $t_{max}$ (h) |
|---|---|---|---|---|---|---|---|---|
| | Ibuprofen – Repeat Dose Day 4 – Mean (± SD) | | | | | | | |
| Treatment A: | 33.14 (6.12) | 0.72 (0.42) | 9.81 (1.96) | 3.44 (0.65) | 62.47 (40.28) | 230.73 (47.00) | 118.12 (24.23) | 1.66[a] |
| Treatment B: | 33.65 (7.32) | 2.64 (1.24) | 13.69 (2.73) | 2.26 (0.50) | 14.9 (8.72) | 328.60 (65.71) | 114.28 (22.77) | 1.53[a] |
| | Paracetamol - Repeat Dose Day 4 - Mean (± SD) | | | | | | | |
| Treatment A: | 16.09 (5.14) | 0.74 (0.35) | 4.07 (1.05) | 3.93 (1.62) | 22.91 (10.05) | 97.67 (25.13) | 51.72 (12.89) | 0.67[a] |
| Treatment B: | 15.87 (5.29) | 1.87 (0.79) | 5.86 (1.88) | 2.47 (0.83) | 8.73 (4.75) | 140.80 (40.30) | 50.74 (13.29) | 0.67[a] |

However, the $C_{min}$ (trough) values after three times daily dosing were higher relative to twice daily dosing (3.7 and 2.5 times for ibuprofen and paracetamol, respectively) and the overall extent of absorption was 1.4 times greater. The three times daily dosing regimen could be considered therefore to provide a more consistent exposure to therapeutic plasma levels of ibuprofen and paracetamol with less fluctuation which might confer more consistent pain relief for the patient.

This study supports:

- That a steady state has been reached and there is a lack of accumulation of ibuprofen and paracetamol.

- The posology for 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' of one tablet to be taken every 6 to 8 hours with a maximum of three tablets in a 24 hours period.

**Pharmacokinetic Conclusion**

There is no apparent pharmacokinetic drug-drug interaction between ibuprofen and paracetamol as evidenced through the demonstration of bioequivalence to the actives when given alone. There is considered to be a significant food effect, the $C_{max}$ and $T_{max}$ being reduced and lengthened respectively in the fed state. This has been reflected accordingly in the SPC.

Repeat dosing with 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' 2 or 3 times a day for 3 days was not associated with drug accumulation, steady state being reached after 4 days. Lower peak to trough variability is seen with a three-times-a-day posology, and this dosing regimen is supported.

These data can be extrapolated to the 1 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' as the pharmacokinetic of ibuprofen and paracetamol are these doses are linear.

**Pharmacodynamics**

No new pharmacodynamic data has been submitted and is not required.

## EFFICACY

The efficacy of ibuprofen and paracetamol alone in the treatment of acute pain has been established through well controlled, randomised clinical studies. In accordance with CPMP/EWP/612/00 guidance on the investigation of medicinal products for the treatment of nociceptive pain a pivotal study has been conducted in a well characterised acute pain model to confirm the efficacy of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and establish superiority over the single actives. In addition a confirmatory pivotal efficacy and tolerability study was conducted in a chronic pain model.

The clinical programme included three randomised, double-blind, parallel group efficacy and tolerability studies (NL0408, NL0604 and NL0605). The exploratory study (NL0408) and the pivotal study (NL0604) both were of a factorial design and placebo-controlled. The pivotal study NL0605 was an active controlled study.

### Exploratory Study NL0408

A double-blind, parallel-group, placebo-controlled randomised, single dose, two centre, modified factorial designed study to compare the analgesic efficacy and tolerability of the concomitant use of 1 or 2 ibuprofen 200 mg tablet(s) and paracetamol 500 mg tablet(s) with the single actives (2 x ibuprofen 200 mg and 2 x paracetamol 500 mg tablets) in the treatment of adults experiencing postoperative dental impaction pain.

The exploratory study was conducted with commercially available treatments of ibuprofen (Advil® tablets) and paracetamol (Tylenol® Extra Strength caplets) taken concomitantly.

The primary objective was to compare the analgesic efficacy using standard outcome measures of pain intensity, pain relief, onset and offset of relief, and a subject global assessment. Planned enrolment for each centre was between 80 and 150 subjects to achieve balanced randomisation between the two centres. A total of 234 subjects were enrolled and randomised into the study (82 at Site 1 and 152 at Site 2). The majority were females (74.4%), and the mean age was 20.8 years (range: 16-31 years). Subjects underwent surgical removal of three or four impacted molar teeth, (two of which had to be mandibular impacted molars requiring bone removal) with a total score of 9 or greater on the impaction grading scale, under local anaesthesia with conscious sedation using standard surgical and sedation techniques. A total of 222 subjects completed the study.

Subjects at each site were stratified by sex and baseline pain intensity. After surgery, subjects rated their pain intensity using a categorical scale and a 100 mm visual analogue scale (VAS). When the pain intensity was rated by the subject as moderate to severe (equal to or greater than 50 mm on the VAS), the subject was randomly allocated in a 2:1:2:1:1 ratio to the following five treatment groups:

- 2 x ibuprofen 200 mg tablets plus 2 x matching paracetamol placebo tablets
- 2 x paracetamol 500 mg tablets plus 2 x matching ibuprofen placebo tablets
- 2 x ibuprofen 200 mg plus 2 x paracetamol 500 mg
- 1 x Ibuprofen 200 mg plus 1 x paracetamol 500 mg plus 1 x matching ibuprofen and 1 x matching paracetamol placebo tablets
- 2 x matching ibuprofen and 2 x matching paracetamol placebo tablets

The 2:1:2:1:1 treatment ratio was used because the most difficult comparison was anticipated to be between the most effective treatments, i.e. 'concomitant ibuprofen 400 mg and paracetamol 1000 mg', and ibuprofen 400 mg.

Subjects were retained in the centre for approximately 10 to 17 hours, including the time before and after surgery and the 8-hour post-dose study period during which pain and safety assessments were performed. Subjects returned for a postoperative visit 5 to 12 days after surgery.

The primary efficacy endpoint, SPRID0-8 (the sum of the pain intensity difference and the pain relief score 0-8 hours) was analysed using an analysis of covariance (ANCOVA), with factors for treatment, study site and sex, and baseline pain intensity. Comparisons between the treatments were assessed at a 2-sided alpha of 0.05. A 95% confidence interval (CI) for the pairwise differences between the two groups was calculated for the parameter estimates of the fitted model. No adjustments for multiple pairwise comparisons were performed.

Pairwise treatment comparisons were made for each of the continuous secondary efficacy variables. These analyses were carried out using ANCOVA; all models included treatment, study site, sex, and baseline pain intensity as factors, and the baseline value for the response variable of interest where appropriate. Where endpoints were aggregated over several timepoints, these were calculated using area-under-the-curve (AUC) as per the primary endpoint.

Differences between treatment groups assessed by time-to-event parameters were assessed using a Cox regression analysis; treatment, study site, sex, and baseline pain intensity were included in each of the models. The relative risk and associated 95% CIs were calculated for the pairwise comparisons.

For binary endpoints, differences between the treatment groups were assessed using logistic regression, with factors for treatment, study site, sex, and baseline pain intensity included. The odds ratios and associated 95% CIs between the treatment group comparisons were calculated.

**Primary Efficacy Endpoint**

The primary population was the intention-to-treat (ITT) population. The term for treatment group ($p < 0.0001$), for gender ($p = 0.014$) and baseline pain intensity ($p = 0.0001$) were statistically significant. The results of the pairwise treatment comparisons performed for the primary endpoint (SPRID0-8) are presented below. The per-protocol population excluded 8 subjects. All comparisons reflected those reported for the ITT analysis.

The results show that 'concomitant ibuprofen 200 mg and paracetamol 500 mg' (e.g. 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet') was statistically significantly superior to paracetamol 1000 mg alone, and placebo, but not to ibuprofen 400mg alone. 'Concomitant ibuprofen 400 mg and paracetamol 1000 mg' was statistically significantly superior to 'concomitant ibuprofen 200 mg and paracetamol 500 mg', placebo, ibuprofen 400 mg alone and paracetamol 1000 mg alone:

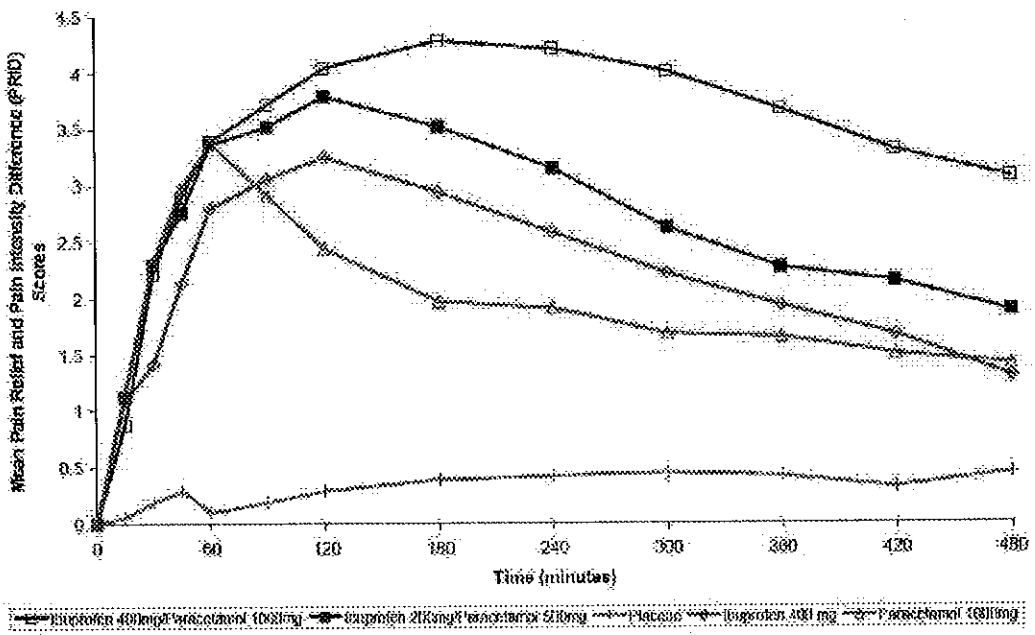
| Treatment group | Primary Endpoint SPRID 0-8h – pairwise treatment comparisons: [a] | | | |
|---|---|---|---|---|
| | 'Concomitant ibuprofen 200 mg and paracetamol 500 mg' | Placebo | Ibuprofen 400 mg | Paracetamol 1000 mg |
| 'Concomitant ibuprofen 200 mg and paracetamol 500 mg' vs. | - | <0.0001*** | NS | 0.0296* |
| 'Concomitant ibuprofen 400 mg and paracetamol 1000 mg' vs. | 0.0209* | <0.0001*** | <0.0001*** | <0.0001*** |
| placebo vs. | <0.0001*** | - | <0.0001*** | 0.0001*** |

Key: SPRID 0-8 h = sum of the pain intensity difference and the pain relief score 0-8 hours. [a] All statistical comparisons are in favour of the higher-dose treatment; * p < 0.05, ** p < 0.01, *** p < 0.001; NS = not statistically significant

For PRID (mean pain relief and pain intensity difference) 'concomitant ibuprofen 200 mg and paracetamol 500 mg' (e.g. 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet') was statistically significantly superior compared to:

- Placebo at all time points.
- Paracetamol 1000 mg alone from 2 to 4 hours post-dose
- Ibuprofen 400 mg alone for the first 30 minutes post-dose

'Concomitant ibuprofen 200 mg and paracetamol 500 mg' was not statistically significantly different to 'concomitant ibuprofen 400 mg and paracetamol 1000 mg' for the first 4 hours post-dose. From 4 to 8 hours post-dose the high dose combination was statistically significantly superior to the lower dose.




The study confirmed that:

- 'Concomitant ibuprofen 200 mg and paracetamol 500 mg', (e.g. 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet') was a more effective analgesic than paracetamol 1000 mg, but was not statistically significantly different to ibuprofen 400 mg alone in the treatment of moderate to severe acute pain.

- 'Concomitant ibuprofen 200 mg and paracetamol 500 mg' was more effective than placebo for all efficacy measures.

- 'Concomitant ibuprofen 400 mg and paracetamol 1000 mg' was a more effective analgesic than ibuprofen 400 mg alone, paracetamol 1000 mg alone and placebo.

- The efficacy data demonstrates a clear dose response between 'concomitant ibuprofen 400 mg and paracetamol 1000 mg' and 'concomitant ibuprofen 200 mg and paracetamol 500 mg'.

**The Pivotal Studies**
The pivotal studies (NL0604 and NL0605) were conducted with the fixed combination product 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. The reference products in NL0604 were the single actives ibuprofen (Advil® tablets) and paracetamol (Tylenol® Extra Strength caplets). The reference products in NL0605 were single actives ibuprofen (Nurofen® caplets) and paracetamol (Panadol® caplets).

Studies NL0408 and NL0604 were conducted using the post-operative dental pain model. The extraction of the third molars is the most common surgical procedure performed in oral surgery practice. Although after surgery, patients can suffer from swelling, bruising, dry socket and a limited ability to open their mouth, the main complication is pain.

Post-operative dental pain is a validated pain model that is a widely accepted and used methodology to evaluate and compare analgesic efficacy. The model is robust as it produces moderate to severe pain that is predictable in character, duration and intensity. In addition, the model is sensitive and has a proven record of separating treatments from each other and placebo. The post-operative dental pain model has been widely used to assess and compare the efficacy of ibuprofen and paracetamol.

Key advantages of the post-surgical dental pain model are population homogeneity (generally young adults in good general health), it is elective, surgery is localised utilising a consistent technique and is generally completed within 30 minutes. Pain onset is usually within 1-3 hours of the surgery and lasts for several hours. Almost all patients will elect to take some form of pain relief.

**Pivotal Study NL0604**
A multicentre randomised, double-blind, parallel-group, placebo-controlled, factorial designed study examining the analgesic efficacy and tolerability of three fixed combination doses of ibuprofen and paracetamol in adult dental pain following third molar extraction. This was a two-part study. Part 1 was a single dose phase where efficacy was assessed following the first dose of study medication to show the factorial effects of the fixed combinations, i.e., the single actives contribution to the overall effect of the fixed combination and dose-response. Part 2 was a multiple dose phase to assess the efficacy and tolerability of the fixed combinations. Safety and tolerability was assessed throughout Part 1 and 2 of the study.

The following fixed combination doses were selected:
• Ibuprofen 400 mg and paracetamol 1000 mg (2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet')
• 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'
• Ibuprofen 100 mg and Paracetamol 250 mg tablet

The following reference products were selected:

- Ibuprofen 400 mg (as 2 x ibuprofen 200 mg tablets)
- Ibuprofen 200 mg tablet
- Paracetamol 1000 mg (as 2 x paracetamol 500 mg tablets)
- Paracetamol 500 mg tablet

Placebo tablets were identical to the respective study medication.

The following measures were used to assess efficacy: Pain intensity (PI) categorical and VAS measurements, pain relief (PAR) categorical measurements, 'pain half gone' categorical measurement, 'perceptible' and 'meaningful pain relief' using the two-stopwatch method, 'subjects' overall assessment' on a categorical scale, and a comparison assessment of the subjects' opinion of the medication taken in Part 1 compared to Part 2.

**Part 1 (Single Dose Phase) Primary Objective**
The primary objective was to show the factorial effects and dose response of the combination of ibuprofen and paracetamol by comparing the total analgesic effect, peak analgesic effect, onset and duration of action, and the subject's overall assessment of the study medication with placebo and the single active reference products.

Subjects were randomly allocated to one of the eight treatment groups and instructed to take their assigned study medication once their rated pain intensity (PI) was "moderate" to "severe" and their visual analogue score (VAS) was equal to or greater than 50 mm.

Subjects were monitored until a second dose of study medication was taken (the first dose of Part 2).

**Part 2 (Multiple Dose Phase) Primary Objective**
The primary objective was to compare the efficacy and tolerability of the fixed combinations by comparing the analgesic effect and the subject's overall assessment of the study medication. In Part 2 there were four treatment groups.

For subjects who had taken the fixed combination tablet or placebo in Part 1, they continued on this treatment (primary population). For subjects who received a single active treatment in Part 1, they received the counterpart combination in Part 2 (secondary population). The subjects took study medication when required.

The first dose of study medication in Part 2 (the second dose of the study) and subsequent doses were taken under the following conditions: at least 8 hours had elapsed after the previous dose of study medication, when the level of pain was 30 mm or greater (VAS), and provided the subject had not consumed more than two doses of first-line rescue medication in the previous 24 hours. Subjects were monitored for approximately 72 hours in Part 2 and returned for an evaluation seven to ten days following surgery.

735 subjects were randomised to receive Part 1 study medication:

- 149 subjects had 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet',
- 143 subjects had 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet',
- 71 subjects had 1 x Ibuprofen 100 mg and Paracetamol 250 mg tablet,
- 74 subjects had 1 x ibuprofen 400 mg,
- 75 subjects had 1 x ibuprofen 200 mg,
- 74 subjects had 1 x paracetamol 1000 mg,
- 76 subjects had 1 x paracetamol 500 mg
- 73 subjects had 1 x placebo.

Of the 735 subjects, 62.6% were female and the mean age was 20.3 years (16-39 years).

The mean duration of surgery was 16.3 minutes. All, but two subjects satisfied the inclusion criteria of at least three impacted third molars (two of which must have been mandibular impacted molars) indicated for removal. Overall the mean VAS for pain was 76.9 mm for all subjects, of which 57.4% experienced severe pain and the remainder experienced moderate pain. The treatment groups were balanced with respect to pain.

Of the 715 subjects that entered Part 2 of NL0604, a total of 658 subjects took at least one dose of study medication in Part 2 (multiple dose phase). A total of 678 subjects completed the multiple dose phase (Part 2) of the study.

**Part 1 (Single Dose Phase) Results for Primary Efficacy Endpoint (SPRID 0-8)**
The primary population was the intention-to-treat (ITT) population. The term for treatment group ($p < 0.0001$), for gender ($p = 0.011$) and centre ($p = 0.02$) were statistically significant, although baseline pain intensity was not ($p = 0.77$). The results for the pairwise comparison for the primary efficacy endpoint (SPRID 0-8h) are summarised below:

| | Primary Endpoint SPRID 0-8h – pairwise treatment comparisons: a | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Ibu 100 mg / Para 250 mg tablet | Placebo | Ibuprofen 200 mg | [200 mg + 400 mg]/ 2 | Ibuprofen 400 mg | Paracetamol 500 mg | [500 mg + 1000mg] /2 | Paracetamol 1000 mg |
| 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' vs. | 0.0169* | <0.0001 *** | 0.0021 ** | 0.0004 *** | 0.0541 | <0.0001 *** | <0.0001 *** | <0.0001 *** |
| Placebo vs. | <0.0001 *** | - | <0.0001 *** | - | <0.0001 *** | 0.0097** | - | <0.0001 *** |

| | Ibuprofen and Paracetamol | | | | |
|---|---|---|---|---|---|
| | 1 x 'Ibuprofen 200 mg / Paracetamol 500 mg tablet' | 100 mg / Paracetamol 250 mg tablet | Placebo | Ibuprofen 400 mg | Paracetamol 1000 mg |
| 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' vs. | NS | 0.0059** | <0.0001*** | 0.0321* | <0.0001*** |
| Placebo vs. | <0.0001*** | <0.0001*** | - | <0.0001*** | <0.0001*** |

Key: SPRID 0-8 h = sum of the pain intensity difference and the pain relief score 0-8 hours. a All statistical comparisons are in favour of the higher-dose treatment; NS = not statistically significant. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

The difference between 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and ibuprofen 400 mg was not significant. The difference between the 1 and 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was not statistically significant.

The study confirmed that:

- 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly superior to ibuprofen 200 mg, paracetamol 500 mg, the non-inferiority measure for ibuprofen and paracetamol, paracetamol 1000 mg, Ibuprofen 100 mg and Paracetamol 250 mg tablet, and placebo.

- The 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly superior to ibuprofen 400 mg, paracetamol 1000 mg and placebo, and Ibuprofen 100 mg and Paracetamol 250 mg tablet.

**Part 2 (Multiple Dose Phase) Results for Primary Efficacy Endpoint (Primary Population)**

The primary endpoint was the 'number of completed 24-hour periods (as 0, 1, 2, 3) with no more than one dose of rescue medication and with the subject's overall assessment always rated as at least good (i.e., 3, 4, 5)'.

The primary analysis was restricted to the primary population, i.e. those subjects randomised to receive combination treatment or placebo throughout Part 1 and 2 of the study. The 11 subjects who withdrew during Part 1 from these four randomised groups were regarded as treatment failures and their values for this endpoint were set to the worst possible value i.e., zero. The 22 subjects who withdrew during Part 2 were also assumed to be treatment failures and therefore their overall assessment was rated as poor and they were considered to have taken more than one dose of rescue medication from the 24-hour period of withdrawal to the end of the 72 hour Part 2 phase inclusive.

Where there was missing data the overall assessment was assumed to be poor. The proportion of missing values was spread evenly across the four randomised groups. The secondary population included all subjects who received a single active in Part 1 and took the corresponding combination in Part 2.

For the primary endpoint, the results for the three fixed combination tablets were similar for the primary population, i.e., 2.29, 2.40, and 2.31 for 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', and 1 x Ibuprofen 100 mg and Paracetamol 250 mg, respectively and 1.00 for placebo.

The first stage compared the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet', and Ibuprofen 100 mg and Paracetamol 250 mg tablet to placebo, which were highly statistically significant ($p < 0.0001$) in favour of the fixed combinations. The next stage compared the three doses of the fixed combination tablets to each other, the differences were not statistically significant, therefore the multiple comparison procedure was stopped.

| | Comparison of number of completed 24-hour periods by treatment* | | |
|---|---|---|---|
| Fixed Combination Tablet | 2 x 'Ibu 200 mg and Para 500 mg tablet' | 1 x 'Ibu 200 mg and Para 500 mg tablet' | 1 x Ibu 100 mg and Para 250mg tablet |
| 2 x 'Ibu 200 mg / Para 500 mg tablet' | - | NS | NS |
| 1 x 'Ibu 200 mg / Para 500 mg tablet' | NS | - | NS |
| 1 x Ibu 100 mg / Para 250 mg tablet | NS | NS | - |
| Placebo | < 0.0001 *** | < 0.0001 *** | < 0.0001 *** |

Key: Ibu = ibuprofen; Para = paracetamol; * with no more than one dose of rescue medication with subjects overall assessment of study medication always rated as at least good; *** $p < 0.001$ using CMH correlation statistic with integer valued table scores and strata according to the cross-classification of gender and baseline pain severity at the start of Part 1

The study confirmed that:

- The fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' at a dose of 1 tablet is more effective than either ibuprofen 200 mg and paracetamol 500 mg alone. The 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' is more effective than ibuprofen 400 mg and paracetamol 1000 mg alone.

- The efficacy of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was sustained over the 8 hour treatment period. A clear dose response was seen between the three doses of the fixed combination where 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was more effective than Ibuprofen 100 mg and Paracetamol 250 mg tablet,

- The efficacy of a 2 tablet dose 2 tablets of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was greater than two tablets of ibuprofen or paracetamol alone (400mg and 1000mg respectively).

**Pivotal Study NL0605 (in chronic pain)**
A multicentre, randomised, double-blind, parallel group, multiple-dose 13 week study designed to demonstrate the overall effectiveness (balance of efficacy and tolerability) of a two doses of the fixed combination 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' in community patients with chronic knee pain.

The study report states:

"It was **not** intended that this protocol be a full factorial design with the ability to discriminate the efficacy of the combination product from that of its individual components, since there is no evidence that knee pain provides enough "upside sensitivity" to show a benefit of paracetamol over and above that of an NSAID. Other studies in post operative pain have also found sensitivity to be an issue. It was inappropriate to use a placebo control for a study in which patients with a painful condition participated for a period of 13 weeks.

The primary reason for conducting this trial was the generation of tolerability and safety data over a treatment period in excess of that proposed for short term non-prescription use and the study was powered to describe tolerability in these terms."

The following fixed combination doses were selected:
• 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'
• 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'

The following reference products were selected:
• Ibuprofen 400 mg (as 2 x ibuprofen 200 mg tablet)
• Paracetamol 1000 mg (as 2 x paracetamol 500 mg tablet)

The study medication was taken three times daily by the participants for 13 weeks.

The primary efficacy objectives were to demonstrate the short-term and long-term efficacy of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' compared to the single actives. The short-term efficacy was the pain element of theWestern Ontario McMaster Universities Osteoarthritis Index (WOMAC) subscale, normalised to 0-100mm visual analogue scale at Day 10, and the long-term efficacy was measured using the patient global assessment of study medication at endpoint (Week 13 using LOCF if there was no Week 13 data). This was assessed on a 5-point Likert scale (excellent, good, fair, poor, unacceptable) in response to the question "Overall, taking into account both how your medicine worked for you and any side effects you think it caused you, how would you rate your medication as a treatment for your painful knee?".

Statistical analysis of the two primary efficacy endpoints was performed using analysis of covariance (ANCOVA) which included factors for treatment, presence of OA, site and baseline WOMAC pain score.

Subjects had to fulfil the criteria of:
- Primary diagnosis of chronic knee pain as evidenced by the presence of pain in or around at least one knee for most days over the last three months and pain on at least four of the seven

days preceding the screening visit. Patients taking analgesic drugs at screening must have been willing to discontinue them.

- Pain of the signal knee, prior to provision of study medication, and, where necessary, after an appropriate washout period on discontinuation of any current analgesic medications, at a level of ≥ 30 mm and ≤ 80 mm on the VAS (pain experienced in the previous 48 hours) for one or more of the following: walking on a flat surface, going up or down stairs, at night while in bed, sitting or lying, standing upright.

In addition, the presence of osteoarthritis had to be confirmed on X-Ray.

Patients had a wash-out period when their normal analgesia was withdrawn, and had to have a specified level of knee pain after washout, before they were eligible for the study. Those with knee pain who were not taking any analgesics but who fulfilled all the entry criteria were also eligible. Randomisation to treatment occurred after washout and only when their knee pain reached the specified level.

Of the 892 subjects randomised, 49% were female and the mean age was 60.6 years (40-84 years). The treatment groups were imbalanced with respect to gender. For the analysis 559 (63%) were considered to have OA. For 57% (507) of subjects the signal knee was the right knee, for three subjects this was not recorded and the remainder it was the left knee. The treatment groups were balanced for effusion in the signal knee, effusion graded as 'bulge', balloon' or 'large tense'. At baseline 64% (569) graded the pain in the previous 48 hours in their signal knee as 'unacceptable if it remained at that level throughout the rest of their life'. The baseline WOMAC pain score overall was 43.6. The baseline pain variables were balanced across the treatment groups. A total of 615 subjects completed the study.

**Results for Primary Efficacy Endpoints**

The full analysis dataset or intention-to-treat (ITT) population was the primary population. As there was a high proportion of missing data a sensitivity analysis was conducted where the missing data was firstly replaced with the baseline observation carried forward (BOCF) and then using the worst possible score. The results of the BOCF analysis were consistent with the principal analysis. The results of the worst case analysis increased the mean differences between the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 1000 mg which were both statistically significant (-5.9; p = 0.02, and -8.9; p = 0.0005 respectively).

| | | Primary Short-term Efficacy (Pain at Day 10)[a] – pairwise treatment comparisons:[b] | | |
|---|---|---|---|---|
| | | 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' | Ibuprofen 400 mg | Paracetamol 1000 mg |
| 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' vs. | Mean difference (95% CI) | - | 0.7 (-2.5, 3.8) | -2.4 (-5.7, 0.8) |
| | p-value | - | NS | NS |
| 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' vs. | Mean difference (95% CI) | -2.9 (-6.0, 0.3) | -2.2 (-5.4, 1.0) | -5.3 (-8.5, -2.1) |
| | p-value | NS | NS | 0.0012** |

Key: [a] Mean WOMAC OA index pain sub-scale scores (normalised 0-100 mm), a lower score is preferable; [b] Estimated from ANCOVA model with factors for treatment, presence of OA and site and a covariate for baseline score. * p < 0.05, ** p < 0.01, *** p < 0.001

For the primary endpoint – long-term efficacy, i.e. 'patient global assessment at endpoint (Week 13 using LOCF for missing data determined on withdrawal)', a total of 880 subjects

provided data and formed the full analysis dataset. A total of 12 subjects (1.3%) had missing data. The term for treatment group (p = 0.002) was statistically significant, although the terms for baseline WOMAC pain score (p = 0.23), presence of OA (p = 0.74) and site (p = 0.22) were not.

The LS mean scores ranked from best to worse, respectively, were: 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (2.54), ibuprofen 400 mg (2.68), 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' (2.69) and paracetamol 1000 mg (2.97).

The results show that the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' were statistically significantly superior to paracetamol 1000 mg alone, but not statistically different to ibuprofen 400 mg alone. Ibuprofen 400 mg alone was statistically significantly superior to paracetamol 1000 mg alone (p = 0.013).

The principal analysis replaced missing data using LOCF which was considered as most appropriate as this was rated on withdrawal from the study. However, a sensitivity analysis was conducted where missing data for all 282 subjects without Week 13 data were firstly replaced with worst possible scores and then using a mixed-effects model repeat measures approach. The results of the worst possible score analysis were consistent with the principal analysis, i.e. the mean differences between the 1 and 2 tablet doses of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 1000 mg were both statistically significant (-0.34; p = 0.02, and -0.51; p = 0.0003 respectively). For the mixed-effect model repeat measures approach the only statistically significant pairwise difference was between 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' and paracetamol 1000 mg (-0.37; p = 0.005).

| | | Primary Long-term Efficacy (patient global assessment at endpoint)* – pairwise treatment comparisons:# | |
|---|---|---|---|
| | | Ibuprofen 400 mg | Paracetamol 1000 mg |
| 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' vs. | Mean difference (95% CI) | 0.01 (-0.22, 0.24) | -0.26 (-0.51, -0.05) |
| | p-value | NS | 0.0152* |
| 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' vs. | Mean difference (95% CI) | -0.14 (-0.37, 0.09) | -0.43 (-0.66, -0.20) |
| | p-value | NS | 0.0002*** |

Key: * Patient global assessment in response to the question "taking into account both how your medicine worked for you and any side effects you think it caused you, how would you rate your medication as a treatment for painful knee?" This was recorded on a 5-point scale where 1 = Excellent, 2 = Good, 3 = Fair, 4 = Poor and 5 = Unacceptable. At Week 13 LOCF was used for missing data; # Estimated from ANCOVA model with factors for treatment, presence of OA and site and a covariate for baseline score. * p < 0.05, ** p < 0.01, *** p < 0.001; Source: Section 14.2, Table 14.2.2.1

The study confirmed that:

- Short-term treatment (at Day 10) with 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' showed no significantly significant difference from either ibuprofen 400mg or paracetamol 1000mg alone in the reduction of knee pain.

- For the primary endpoint the long-term efficacy of 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' was statistically significantly superior compared to paracetamol 1000 mg alone.

- There is evidence of a dose response with the 2 tablet dose of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' being statistically significantly more effective than paracetamol 1000 mg but not compared to ibuprofen 400 mg alone.

The efficacy component of this trial failed to demonstrate that short-term treatment (at Day 10) with 1 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' showed any significantly significant difference from either ibuprofen 400mg or paracetamol 1000mg alone in the reduction of knee pain. 2 x 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' showed a significant improvement to 1g paracetamol only, not ibuprofen 400mg

As stated in the guideline on fixed combination medicinal products (CPMP/EWP/240/95) Section 4.4.1: "the proposed dosage regimen must be justified. The dosage of each substance within the fixed combination must be such as....the benefit/ risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone".

A 400mg dose of ibuprofen is considered routine: the UK SPC for Nurofen 200mg tablets states that an 'initial dose is two tablets'. Therefore, it is assessed that the correct comparator in this instance is ibuprofen 400mg alone, along with the paracetamol 1000mg dose alone for the same reason.

Study NL 0604 shows that a 2 tablet dose shows greater efficacy than two tablets of ibuprofen or paracetamol alone (400mg and 1000mg respectively). Therefore, the requirements of the guidelines are considered fulfilled in this instance in terms of demonstrating the efficacy of the fixed combination.

**SAFETY**

In terms of treatment-related adverse events (AEs) (i.e. those with a definite, probable or possible relationship to therapy), the incidence rates were 51% (236 events) in the higher dose combination group, 50% (240 events) in the lower dose combination group, 45% (196 events) in the paracetamol 1000mg group and 42% (181 events) in the ibuprofen 400mg group. Not allowing for multiple comparisons, the proportion of patients in the higher dose combination group reporting treatment-related AEs was statistically significantly higher than the proportion of ibuprofen 400mg patients reporting such AEs (p=0.04).

A smaller proportion of severe AEs, 51/563 (9%), was reported in the paracetamol 1000mg treatment group, compared to 68/508 (13%) in the ibuprofen 400mg group, 73/579 (13%) in the lower dose combination group and 91/638 (14%) in the higher dose combination group. Overall, 39 (2%) of AEs were classed as definitely related to the study drug, these being spread evenly between the four randomised treatment groups. Forty-one percent of AEs in the lower dose combination group were treatment-related, compared to 37% in the higher dose combination group and 35% in each of the other two randomised groups.

For treatment-related AEs, the three most commonly reported during the study were dyspepsia (142 reports), diarrhoea (67 reports) and nausea (56 reports). There was one death in this study. Patient randomisation number 223 collapsed at home was hospitalised, and died in hospital. The cause of death was a ruptured abdominal aortic aneurism. The patient was in the ibuprofen 400mg treatment group. Causality was assessed by the Investigator as "possible".

Overall, treatment with the higher dose combination is associated with an increase in the number of adverse events compared to the use of either ibuprofen or paracetamol alone. The profile of events is similar in each treatment group, the difference being an increase in gastrointestinal events. Most of these events did not require medical intervention and resolved on withdrawal of treatment.

Treatment with the lower dose combination was associated with a smaller increase in adverse event incidence that was not statistically significant when compared to ibuprofen alone or paracetamol alone. The profile of events in the lower dose combination group was similar to that of ibuprofen alone and paracetamol alone suggesting the risks associated with this treatment are similar to those of ibuprofen alone and paracetamol alone.

The study confirmed that:

- There were a greater number of adverse events seen with the two tablet dose compared with the use of paracetamol or ibuprofen alone. However these adverse events were mild in nature and self limiting.

- The profile of adverse events is similar whether the treatments are taken alone or in combination and most of these events do not requiring medical intervention, resolving on withdrawal of treatment. This applies also to the higher dose combination, although the higher dose strength is associated with an increase in the number of adverse events compared to the use of either ibuprofen or paracetamol alone.

**Post marketing experience**

The combination of ibuprofen and paracetamol in a single tablet has not previously existed in the EEA. In countries such as India, Russia, Poland, South Africa and continents such as Asia and South America, the fixed combination of ibuprofen and paracetamol has been licensed at varying maximum daily doses (ibuprofen 1.2–2.4 g and paracetamol 1.3–2.6 g) for the treatment of pain and fever. One product in India and one in Thailand contain the same dose combination as 'Ibuprofen 200 mg and Paracetamol 500 mg tablet'. However, accurate pharmacovigilance data on the Indian product is not available in the public domain and the data is not collected by the authorities in Thailand.

As in many other countries in the world, there is a practice of co-prescribing ibuprofen and paracetamol in the UK. Therefore the Applicant commissioned a pharmacoepidemiology study utilising data from the UK General Practice Research Database (GPRD) with the intention to investigate potential safety issues and highlights potential areas to focus on in non-prescription usage. The subset of data, from the GPRD study, that is most closely aligned with the proposed non-prescription usage of 'Ibuprofen 200 mg and Paracetamol 500 mg tablet' by dose, duration (≤ 2 weeks), and number of prescription less than or equal to 1-5 prescriptions showed that the safety outcomes were similar to those for the single actives and highlight no new potential issues.

## SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

## CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

## MAA FORM

The MAA Form is medically satisfactory.

## CONCLUSIONS

It is recommended that a Marketing Authorisation is granted for this application.

# IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

## QUALITY

The important quality characteristics of Nuromol 200mg/500mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

## NON-CLINICAL

No new preclinical data were submitted and none are required for an application of this type.

## CLINICAL

The risk benefit is considered positive and a Marketing Authorisation can be recommended from the clinical point of view.

## RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ibuprofen and paracetamol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

# Module 5

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

**NOTE - Entire 36 page document removed**

**CONFIDENTIAL**

[redacted]

Read the enclosed leaflet before taking this product.
Each tablet contains: Ibuprofen 200mg and Paracetamol 500mg

FOR RELIEF FROM:
- Headache
- Rheumatic and muscular pain
- Period pain
- Cold and flu symptoms
- Back ache
- Sore throat and fever
- Dental pain
- Migraine
- Pain of non-serious arthritic conditions

DO NOT TAKE IF YOU:
- Have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- Are allergic to ibuprofen, paracetamol or any other ingredient of the product, aspirin or other related painkillers
- Are taking other NSAID painkillers or aspirin with a daily dose above 75mg

CONTAINS PARACETAMOL.
Do not take with any other paracetamol-containing product. Immediate medical advice should be sought in the event of an overdose, even if you feel well.

SPEAK TO A PHARMACIST/DOCTOR BEFORE TAKING IF YOU:
- Have or have had asthma, diabetes, high cholesterol, high/low blood pressure, a stroke, heart, liver, kidney or bowel problems
- Are a smoker
- Are pregnant

DOSAGE:
For oral administration and short term use only.
Take 1 tablet (or 2 if required), up to 3 times daily with food.
Do not exceed 6 tablets in 24 hours and leave 6 hours between doses.
Do not give to children under 18 years.
If symptoms persist or worsen, consult your doctor.
Do not take for more than 3 days.

WARNING: Do not exceed the stated dose

KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.

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BETTER HEALTH THROUGH RESPONSIBLE SELF CARE

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- Consumer Medicine Information
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- Complaints about Advertising


# Self Care Products

Non-prescription medicines can be bought without a doctor's prescription. Most can be bought in a pharmacy. Some can be bought in outlets such as supermarkets or health food stores.

They include over-the-counter medicines and complementary medicines, such as vitamins and minerals, herbals, homoeopathic and aromatherapy products.

The 'schedule' of a self care product determines where it can be sold:

- Products labelled 'Pharmacist-Only Medicine' can only be bought in a pharmacy. They are usually stored in the dispensary. The pharmacist is required to be involved in the sale to provide advice and to ensure that the medicine is appropriate for the consumer.

  These products are also called Schedule 3 medicines or over-the-counter medicines.

- Those labelled 'Pharmacy Medicine' can only be bought in a pharmacy, but can usually be self-selected by the consumer. The pharmacist is available to provide advice if it is requested by the consumer.

  These products are also called Schedule 2 medicines or over-the-counter medicines.

- Unscheduled or general sale over-the-counter and complementary medicines can be bought either in pharmacies or from other outlets such as supermarkets and health food stores.

Unless otherwise recommended, self care products are only for short-term use.

**Indications/conditions**

Self care products are available to help treat or relieve symptoms of a large range of indications and conditions. The following list gives examples:

- Allergy and hayfever
- Coughs and colds, including sore throats and fever
- Motion/travel sickness
- Smoking cessation
- Sleeping aids
- Pain relief, e.g.
  - headache
  - dental pain
  - arthritic and joint pain
  - menstrual pain
  - migraine
  - muscular pain, including sprains and strains
- Eye, ear and mouth conditions, e.g.
  - conjunctivitis
  - sore, tired eyes
  - ear wax and swimmer's ear
  - baby teething
  - dental hygiene

    - mouth ulcers
- Gastro-intestinal disorders, e.g.
    - antacids for heartburn and indigestion, nausea and upset stomach
    - infant colic/gripe
    - constipation
    - diarrhoea
    - irritable bowel syndrome, including flatulence or wind
    - haemorrhoids
    - worms
- Skin and scalp conditions, e.g.
    - acne and pimples
    - antiseptics for first aid use
    - baby care, including nappy rash and cradle cap
    - cold sores
    - corns and warts
    - dandruff
    - dry skin, eczema and psoriasis
    - footcare
    - fungal infections, such as tinea/athletes foot, ringworm
    - hair loss and baldness
    - head lice
    - insect bites and stings
    - rashes
    - scabies
    - skin allergies, hives and itching
    - sunscreens and sunburn
- Urinary and gynaecological conditions, e.g.
    - cystitis – a bladder inflammation with frequent and burning urination
    - menstrual pain
    - vaginal thrush

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# Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are widely used analgesics in the prescription and non-prescription settings. Although both classes of drug are generally well tolerated, they can lead to well-characterized adverse effects. Both drugs are widely co-prescribed and it is of interest to understand better safety outcomes when the two drugs are taken concomitantly.

## WHAT THIS STUDY ADDS?

Relative rates and hazard ratio patterns of safety outcomes were broadly similar for patients prescribed ibuprofen alone, paracetamol alone and concomitant ibuprofen and paracetamol. The risks of the various safety outcomes examined do not appear to be modified by concomitant use of ibuprofen and paracetamol compared with paracetamol or ibuprofen alone.

## AIMS

To evaluate and compare the risk of specific safety outcomes in patients prescribed ibuprofen and paracetamol concomitantly with those in patients prescribed ibuprofen or paracetamol alone. The outcomes were evaluated according to dose, duration and exposure.

## METHODS

The study used a retrospective longitudinal cohort design with data from the UK General Practice Research Database (GPRD). The study population included patients aged 18 years or over who were prescribed ibuprofen alone, paracetamol alone or concomitant ibuprofen and paracetamol (tablets or capsules only). 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. Time-dependent Cox regression was used to estimate relative rates for the safety outcomes, by treatment group. A further analysis evaluated whether the hazard rates (i.e. absolute risks) varied over time with changes in drug exposure.

## RESULTS

The study population included 1.2 million patients. There was considerable heterogeneity in both patient and exposure characteristics. When comparing with past users, for most safety outcomes, current users of concomitant paracetamol and ibuprofen had relative rates between those for current users of ibuprofen alone and paracetamol alone. The hazard rates were generally proportional over time, from current to past exposure, following a prescription for concomitant paracetamol and ibuprofen compared with ibuprofen alone or paracetamol alone.

## CONCLUSIONS

The known risk of the safety outcomes examined does not appear to be modified by concomitant use of ibuprofen and paracetamol compared with paracetamol or ibuprofen alone.

## Introduction

Ibuprofen and paracetamol are widely used analgesics. Although both drugs are readily available as over the counter (OTC) medications, they are also available on prescription. Although nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are generally well tolerated, infrequent but potential adverse effects include upper gastrointestinal (GI) bleeding and perforation, renal failure and heart failure [1]. The objective of this retrospective cohort study was to evaluate a range of safety outcomes in patients prescribed ibuprofen and paracetamol concomitantly and compare these with safety outcomes in patients prescribed ibuprofen or paracetamol alone. Specifically, these outcomes were assessed with reference to the dosage and treatment duration.

## Methods

### Data source

The study data was sourced from the UK General Practice Research Database (GPRD). The GPRD contains anonymized computerized medical records from general practitioners (GPs). The records include demographic information, prescription details, clinical events, provision of preventive care, details of specialist referrals and hospital admissions and major outcomes [2, 3]. The GPRD data collection started in 1987 and currently includes data on approximately 10 million patients (http://www.gprd.com/home).

### Study population

The study cohort included patients aged 18 years or older who received a prescription for ibuprofen or paracetamol (tablets or capsules only) between 1987 and August 2007. The date of the first prescription of ibuprofen or paracetamol during this data collection period was defined as the index date. The follow-up period was from the index date to August 2007 or the date the patient transferred out of the practice, or the date of death, whichever was earliest. The study was reviewed scientifically by the Independent Scientific Advisory Committee of GPRD and approval by the Trent ethics committee was given for research with anonymized GPRD data.

### Safety outcomes

Safety outcomes were assessed with OXMIS and Read codes, and included: mortality, upper GI events (gastroduodenal ulcers and complications such as upper GI haemorrhage), myocardial infarction (MI), stroke, acute renal failure, congestive heart failure, overdose (intentional or accidental) and suicidal behaviour. Suicidal behaviour included self-laceration, overdose (irrespective of the type of chemical) or suicidal thoughts. These medical terms are based on those used by Martinez and colleagues [4] in another GPRD study.

### Exposure definitions

The total period of follow-up was divided into periods of 'current', 'recent' and 'past' exposure using the following definitions: current exposure, the period from date of the prescription to 3 months after the estimated end of the prescription; recent exposure, the period 3–6 months after the estimated end of the prescription; past exposure, the period ≥6 months after the estimated end of the prescription. Each exposure period was then classified into 'ibuprofen only', 'paracetamol only' and 'concomitant paracetamol and ibuprofen' using the following definitions: (i) ibuprofen only, with no prescriptions for paracetamol, other NSAIDs and aspirin in the preceding 6 months, (ii) paracetamol only, with no prescriptions for ibuprofen, other NSAIDs and aspirin in the preceding 6 months and (iii) concomitant paracetamol and ibuprofen prescribed on the same date, with no prescriptions for other NSAIDs and aspirin in the preceding 6 months. As exposure may vary over time, patients were classified in a time-dependent manner with patients moving between exposure categories over time.

In order to evaluate the association between outcomes and frequency of exposure, current users were classified into seven groups based on the exposure characteristics: (i) first prescription (Rx), patients who received their first ibuprofen or paracetamol prescription at least 12 months after the start of GPRD data collection and who had not previously been prescribed aspirin or other NSAIDs, (ii) long gap, patients with at least 6 months between a preceding prescription for ibuprofen, paracetamol, aspirin or other NSAID and the current prescription for ibuprofen, paracetamol or concomitant ibuprofen and paracetamol, (iii) repeat use with a low medication possession ratio (MPR), for patients who had been prescribed ibuprofen and/or paracetamol in the preceding 6 months. The MPR is defined as the ratio of duration of the previous prescription, to the time between that prescription and the current prescription (equal to <0.40), (iv) repeat use with a medium MPR, as above but with ratio equal to 0.40–0.59, (v) repeat use with a high MPR, as above but with ratio equal to 0.60–0.79, (vi) repeat use with a very high MPR, as above but with ratio equal to >0.8 and (vii) repeat use with no information on the number of days prescribed, and consequently no information on compliance.'

### Statistical analyses – relative rates of safety outcomes

Poisson regression models were used to estimate the relative rates (RRs and 95% confidence intervals) of the safety outcomes in current users of ibuprofen alone, paracetamol alone or concomitant ibuprofen and paracetamol. The RRs were adjusted for age, gender, calendar year, body mass index, smoking history, alcohol use, number of visits to the GP in the previous 6–12 months, hospital admission in the

previous year and socioeconomic status in the location of the practice. Prescribing of other types of NSAIDs or aspirin in the preceding 6 months was also noted. Additional risk factors in the statistical adjustment specific for each of the safety outcomes included: (i) for mortality, the additional risk factors were a history of: upper GI events, osteoarthritis, rheumatoid arthritis, ischaemic heart disease, heart failure, hypertension, cerebrovascular disease, diabetes mellitus, hyperthyroidism, stroke or transient ischaemic attack, cancer (excluding non-melanoma skin cancer), inflammatory bowel disease, autoimmune disease (systemic lupus erythematosus, systemic sclerosis, vasculitis, rheumatoid arthritis), depression, drug abuse and prescribing in the previous 6 months (anticoagulants, oral glucocorticoids, diuretics, cardiac glycosides, statins, angiotensin receptor blockers, hypnotics and anxiolytics, antipsychotic drugs, antibacterial drugs, aminosalicylates, antidepressants), (ii) for upper GI events, the additional risk factors were a history of upper GI events, osteoarthritis or rheumatoid arthritis, prior prescribing of anticoagulants, aspirin, oral corticosteroids, proton pump inhibitors, $H_2$-receptor antagonists, (iii) for MI, the additional risk factors were a history of ischaemic heart disease, heart failure, hypertension, cerebrovascular disease, diabetes mellitus, hyperthyroidism, hyperlipidaemia, prior prescribing of diuretics, cardiac glycosides, statins, angiotensin receptor blockers, oral glucocorticoids, (iv) for stroke, the additional risk factors were a medical history of stroke or transient ischaemic attack, heart failure, hypertension, cerebrovascular disease, diabetes mellitus, hyperthyroidism, hyperlipidaemia, prior prescribing of diuretics, cardiac glycosides, statins, angiotensin receptor blockers, anticoagulants, oral glucocorticoids, (v) for heart failure, the additional risk factors were a history of ischaemic heart disease, hypertension, cerebrovascular disease, diabetes mellitus, hyperthyroidism, prior prescribing of diuretics, cardiac glycosides, statins, angiotensin receptor blockers, oral glucocorticoids, (vi) for renal failure, the additional risk factors were a history of cancer (excluding non-melanoma skin cancer), congestive heart failure, inflammatory bowel disease, autoimmune disease (systemic lupus erythematosus, systemic sclerosis, vasculitis, rheumatoid arthritis), diabetes mellitus, hypertension, prior prescribing of hypnotics and anxiolytics, antipsychotics, antibacterials, aminosalicylates, oral glucocorticoids and (vii) for overdose or suicidal behaviour, the additional risk factors were a history of depression, drug abuse, prior prescribing of antidepressants, antipsychotics.

### *Pattern of risk over time following a prescription*

Hazard rates (i.e. absolute risk) were estimated over time following a prescription. The follow-up period was from the date of the prescription until the date of the next prescription or date of censoring, whichever was earliest. The total follow-up period was divided into 100 sub-periods and the absolute risk was estimated within each sub-period. These estimates were then smoothed using the methods proposed by Ramlau-Hansen [5]. For computational reasons, the hazard rates were estimated for a maximum of 100 000 prescriptions and random subsamples were used for larger numbers. This analysis of hazard rates can be used to display visually the observed (crude) risks over time. The time close to a prescription is likely to include the greatest number of patients exposed to the drug, while the distant time is likely to include more patients who discontinued the drug. In traditional epidemiological studies, the time close to a prescription would be classified as current exposure and distant time as past exposure. Changes in rates over time (i.e. testing whether rates remained parallel over time or diverged/converged) were evaluated using the test for proportionality in Cox proportional hazards regression. Age, sex and calendar year at the time of the prescription were included in the regression analysis. This method has previously been used to study hazard rates of MI and mortality in users of $\beta_2$-adrenoceptor agonists [6, 7].

## Results

The study population included 1.2 million patients. Of these, 1.0 million had not been prescribed other NSAIDs or aspirin in the preceding 6 months. At the index date, mean ages were 47.5 years in the ibuprofen group, 62.5 years in the paracetamol group and 52.5 years in the concomitant ibuprofen and paracetamol group (Table 1). Patients in the paracetamol alone group were more likely to be on concomitant medication or have history of disease.

From the index date onwards, Table 2 shows that the patient population and the frequency of prescribing ibuprofen and/or paracetamol were different between groups. Ibuprofen alone was prescribed to a younger population (mean age 57.0 years) and less frequently than paracetamol alone (mean age 71.6 years) or concomitant ibuprofen and paracetamol (mean age 64.6 years).

As shown in Table 3, current users with continuous use (very high MPR) of ibuprofen (e.g. RR stroke 1.23, 95% CI 1.12, 1.35) or paracetamol (e.g. RR stroke 1.30, 95% CI 1.19, 1.41) generally had higher RRs, and those with intermittent drug use (low MPR) had lower RRs (e.g. RR stroke in ibuprofen users 0.99, 95% CI 0.86, 1.13; RR stroke in paracetamol users 1.03, 95% CI 0.97, 1.10) compared with past users. The RRs of most outcomes were statistically similar in current users of ibuprofen alone, paracetamol alone and concomitant ibuprofen and paracetamol (based on the tests for interaction between the RRs). The RRs for the safety outcomes were statistically proportional over time, from current to past exposure, between the various medication classes, with the exception of renal failure (based on the tests for proportionality of RR over time). Figure 1 gives the crude hazard rates for each safety outcome following a

## Table 1

Characteristics of study population at baseline (index date)

| Characteristic, *n* (%) | Drug exposure at baseline | | |
|---|---|---|---|
| | Ibuprofen alone (*n* = 806 381) | Paracetamol alone (*n* = 382 404) | Concomitant ibuprofen and paracetamol (*n* = 13 079) |
| **Mean duration of follow-up (years)** | 6.9 | 4.4 | 3.8 |
| **Number of women** | 456 996 (57) | 246 080 (64) | 8187 (63) |
| **Mean age (years)** | 47.5 | 62.5 | 52.5 |
| **Age (years) (%)** | | | |
| **18–39** | 308 159 (38) | 79 825 (21) | 4605 (35) |
| **40–64** | 321 524 (40) | 76 045 (20) | 3536 (27) |
| **≥65** | 176 698 (22) | 226 534 (59) | 4938 (38) |
| **Body mass index, *n* (%)** | | | |
| **<20** | 44 925 (6) | 26 352 (7) | 848 (6) |
| **20–25** | 256 889 (32) | 100 171 (26) | 3692 (28) |
| **25–30** | 234 429 (29) | 96 375 (25) | 3382 (26) |
| **>30** | 131 897 (16) | 61 239 (16) | 2251 (17) |
| **Unknown** | 138 241 (17) | 98 267 (26) | 2906 (22) |
| **Medication used in preceding 6 months, *n* (%)** | | | |
| **Anticoagulants** | 2 426 (<1) | 14 721 (4) | 97 (1) |
| **Antidepressants** | 67 823 (8) | 57 304 (15) | 1713 (13) |
| **Angiotensin receptor blockers** | 33 492 (4) | 50 347 (13) | 980 (7) |
| **Antipsychotics** | 24 471 (3) | 30 833 (8) | 561 (4) |
| **Acetylsalicylic acid** | 38 896 (5) | 70 674 (18) | 1248 (10) |
| **Cardiac glycosides** | 5 725 (1) | 18 311 (5) | 180 (1) |
| **Diuretics (any)** | 74 938 (9) | 103 599 (27) | 1943 (15) |
| **NSAIDs** | 94 142 (12) | 126 662 (33) | 2331 (18) |
| **Oral corticosteroids** | 13 590 (2) | 21 332 (6) | 312 (2) |
| **Disease history, *n* (%)** | | | |
| **Cancer excluding skin cancer** | 20 243 (3) | 26 492 (7) | 702 (5) |
| **Heart failure** | 8 801 (1) | 22 940 (6) | 297 (2) |
| **Ischaemic heart disease** | 39 761 (5) | 55 383 (14) | 871 (7) |
| **Cerebrovascular disease** | 16 095 (2) | 33 316 (9) | 460 (4) |
| **Depression** | 133 198 (17) | 76 287 (20) | 2753 (21) |
| **Diabetes mellitus** | 30 290 (4) | 34 634 (9) | 788 (6) |
| **Substance abuse** | 12 970 (2) | 12 442 (3) | 455 (3) |
| **Osteoarthritis** | 75 640 (9) | 73 922 (19) | 1917 (15) |
| **Autoimmune disease** | 9 303 (1) | 11 411 (3) | 237 (2) |
| **Upper gastrointestinal disease** | 16 568 (2) | 23 664 (6) | 271 (2) |

Percentages may not add up to 100% due to rounding. NSAIDs, non-steroidal anti-inflammatory drugs.

prescription, which were used in the statistical proportionality analysis.

## Discussion

This study used data from the GPRD to evaluate the safety of concomitantly prescribed ibuprofen and paracetamol, ibuprofen alone and paracetamol alone. There was considerable between-group heterogeneity in the patient and exposure characteristics. An analysis of patterns of risks for safety outcomes over time and changes in exposure was conducted partly to overcome the issues of unmeasured confounding and bias in the study population.

### *Mortality*

The RR of mortality had a U-shaped pattern in all medication classes, with a larger excess in patients without extensive prior use of ibuprofen or paracetamol and in patients with long-term continuous use of the same medication class. The most likely explanation for the higher risk in patients without extensive prior use is that these drugs were prescribed to patients with severe disease at increased risk of death. Patients with pain symptoms due to an exacerbation of a severe disease may have been more likely to visit the GP and be prescribed an analgesic. Large studies conducted in Denmark found similar confounding by indication with ibuprofen and, particularly, paracetamol [8, 9]. The pattern of mortality risk over time showed that concomitant use of ibuprofen and paracetamol was statistically comparable with that of ibuprofen and paracetamol alone. The differences between these groups were of similar magnitude during current and past exposure, which does not support the presence of differential effects on mortality of these analgesics.

**Table 2**

Frequency of exposure for patients defined as current users of ibuprofen alone, paracetamol alone and concomitant ibuprofen and paracetamol overall and stratified by exposure characteristics

| Exposure characteristics | | Ibuprofen alone (*n* patients = 780 003) (*n* prescriptions = 2 400 082) | | | | Paracetamol alone (*n* patients = 363 177) (*n* prescriptions = 2 549 372) | | | | Concomitant ibuprofen and paracetamol (*n* patients = 37 079) (*n* prescriptions = 117 443) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | % of Rx | Mean age (years) | Women (%) | Repeat NSAID Rx* (%) | % of Rx | Mean age (years) | Women (%) | Repeat NSAID Rx* (%) | % of Rx | Mean age (years) | Women (%) | Repeat NSAID Rx* (%) |
| **All** | | 100 | 57.0 | 60.8 | 50.2 | 100 | 71.6 | 70.6 | 76.0 | 100 | 64.6 | 68.8 | 76.3 |
| **First Rx** | | 18.1 | 44.7 | 53.5 | 11.5 | 4.9 | 56.9 | 63.6 | 21.1 | 6.0 | 46.9 | 59.1 | 20.6 |
| **Long gap** | | 20.6 | 51.6 | 62.1 | 16.8 | 9.9 | 65.6 | 71.1 | 31.1 | 11.8 | 54.1 | 69.6 | 29.6 |
| **Medication possession ratio** | Low | 15.1 | 58.0 | 63.4 | 46.7 | 35.8 | 71.4 | 70.8 | 73.6 | 14.5 | 61.9 | 68.7 | 62.5 |
| | Medium | 10.4 | 62.3 | 62.5 | 71.1 | 20.9 | 74.0 | 70.5 | 90.9 | 12.2 | 66.6 | 68.7 | 84.1 |
| | High | 8.8 | 63.4 | 61.9 | 79.5 | 9.7 | 73.9 | 70.0 | 92.0 | 10.4 | 67.5 | 68.8 | 89.6 |
| | Very high | 27.0 | 64.7 | 62.1 | 85.7 | 18.9 | 75.1 | 72.0 | 93.2 | 45.1 | 69.5 | 70.1 | 94.7 |

*Within 3 months. Percentages may not add up to 100% due to rounding. NSAIDs, non-steroidal anti-inflammatory drugs; Rx, prescription.

## *Upper GI events*

NSAIDs are known to cause upper GI events [1]. In this study, observed RRs (1.18, 95% CI 1.13, 1.24) tended to be lower than those reported previously [10, 11]. A UK study conducted using data from another GP database reported an odds ratio of 1.42 (95% CI 1.27, 1.59) for ibuprofen [11], while an older study reported a RR for ibuprofen of 2.5 (95% CI 1.9, 3.4) [10]. The differences between recent and older estimates for the GI effects of ibuprofen may reflect the increased concomitant use of acid suppressants and/or the substantial reduction over calendar time in the rate of upper GI events [12].

A Canadian study including over 640 000 patients showed that the combination of a standard NSAID and paracetamol was associated with an increased risk of hospitalization for upper GI events [13]. Patients prescribed paracetamol alone were more likely to be older and to have other concomitant disease compared with those prescribed standard NSAIDs alone [14].

Various characteristics of NSAID exposure were measured in our study. Although the GPRD does not contain data on the actual use of medications by patients, a low medication possession ratio may indicate intermittent use (i.e. insufficient medication for continuous use). We found that the rate of upper GI events was higher in those patients with frequent NSAID use. A US case-control study in which patients were interviewed about their medication use found no increased risk of upper GI events with infrequent NSAID use (either OTC or prescription), while frequent use was associated with a doubling of risk [15]. These findings indicate that comparisons between different analgesics should take into account exposure characteristics.

## *Cardiovascular events*

Use of paracetamol at high dose or frequency has been associated with an increased risk of cardiovascular events [16]. Adverse cardiovascular effects have also been reported in randomized trials for selective COX-2 inhibitors [16–19]. However, patients included in randomized trials for selective COX-2 inhibitors are very different from patients in daily practice with respect to indications for analgesic use, daily dose and duration of use. The daily dose in patients using selective COX-2 inhibitors was two- to three-fold lower in the GPRD than in major RCTs [12]. Since 2004, there has been growing concern that some of the older NSAIDs, such as diclofenac, may have adverse cardiovascular effects similar to those of selective COX-2 inhibitors [20]. However, there are several challenges in establishing the causal contribution of NSAIDs to cardiovascular outcomes in daily clinical practice. Furthermore, a recent GPRD study found that patients who stopped NSAIDs after a long duration of use were at increased risk of MI [21].

In this study, we found no differences in the rate of MI between the three groups. However, the risk of MI was

## Table 3

Adjusted RR of safety outcomes during current exposure compared with past exposure (of same medication class) overall and stratified by exposure characteristics

| | | | Exposure characteristics | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Medication possession ratio | | | | |
| Safety outcome | Exposure | Overall RR (95% CI) [*n*] | First Rx RR (95% CI) [*n*] | Long gap RR (95% CI) [*n*] | Low RR (95% CI) [*n*] | Medium RR (95% CI) [*n*] | High RR (95% CI) [*n*] | Very high RR (95% CI) [*n*] | Proportionality of hazard rates in the 3 years following a prescription[†] |
| **Upper GI** | Ibuprofen alone | 1.18 (1.13, 1.24) [1 932] | 1.19 (1.05, 1.33)* [293] | 1.15 (1.03, 1.29) [317] | 1.04 (0.91, 1.19) [218] | 0.88 (0.73, 1.05)* [114] | 1.29 (1.08, 1.53) [130] | 1.61 (1.46, 1.78)* [440] | = |
| | Paracetamol alone | 1.36 (1.31, 1.41) [3 033] | 1.74 (1.53, 1.99) [235] | 1.30 (1.17, 1.46) [336] | 1.11 (1.04, 1.21) [824] | 1.25 (1.12, 1.38) [399] | 1.49 (1.29, 1.71) [208] | 1.49 (1.34, 1.66) [367] | = |
| | Concomitant ibu + para | 1.70 (1.32, 2.19) [122] | 2.27 (1.09, 4.72) [8] | 1.45 (0.75, 2.81) [10] | 1.02 (0.51, 2.05) [9] | 1.93 (1.04, 3.57) [12] | 1.43 (0.66, 3.13) [7] | 2.10 (1.40, 3.17) [37] | Reference |
| **Myocardial infarction** | Ibuprofen alone | 1.09 (1.04, 1.14) [1 688] | 0.94 (0.81, 1.09) [181] | 1.22 (1.09, 1.37) [301] | 1.06 (0.93, 1.21) [237] | 1.04 (0.89, 1.22) [158] | 1.25 (1.07, 1.47) [151] | 1.07 (0.97, 1.19) [368] | = |
| | Paracetamol alone | 1.14 (1.10, 1.19) [2 761] | 1.42 (1.22, 1.65) [177] | 0.98 (0.86, 1.11) [254] | 1.11 (1.02, 1.19) [860] | 1.17 (1.05, 1.29) [407] | 1.04 (0.89, 1.23) [157] | 1.17 (1.04, 1.32) [313] | = |
| | Concomitant ibu + para | 1.12 (0.86, 1.46) [88] | 1.31 (0.48, 3.60) [4] | 0.97 (0.42, 2.23) [6] | 1.03 (0.53, 2.01) [10] | 0.80 (0.35, 1.85) [6] | 0.65 (0.24, 1.80) [4] | 1.18 (0.75, 1.87) [28] | Reference |
| **Stroke** | Ibuprofen alone | 1.11 (1.06, 1.16) [1 757] | 1.08 (0.94, 1.25) [187] | 0.91 (0.79, 1.04) [214] | 0.99 (0.86, 1.13) [227] | 1.01 (0.87, 1.18) [166] | 1.13 (0.96, 1.33) [148] | 1.23 (1.12, 1.35) [493] | = |
| | Paracetamol alone | 1.14 (1.10, 1.18) [4 285] | 1.17 (1.02, 1.35) [214] | 1.14 (1.03, 1.25) [453] | 1.03 (0.97, 1.10) [1248] | 1.17 (1.08, 1.27) [655] | 1.02 (0.89, 1.15) [249] | 1.30 (1.19, 1.41) [600] | = |
| | Concomitant ibu + para | 1.30 (1.01, 1.66) [121] | 1.72 (0.69, 4.25) [5] | 1.32 (0.66, 2.65) [9] | 1.15 (0.62, 2.12) [12] | 1.19 (0.61, 2.31) [10] | 1.03 (0.47, 2.25) [7] | 1.40 (0.94, 2.09) [38] | Reference |
| **Heart failure** | Ibuprofen alone | 1.08 (1.03, 1.12) [2 314] | 1.04 (0.91, 1.19) [218] | 1.11 (0.98, 1.25) [286] | 0.89 (0.79, 1.01) [252] | 1.02 (0.89, 1.16) [213] | 1.22 (1.06, 1.40) [212] | 1.31 (1.21, 1.42) [707] | = |
| | Paracetamol alone | 1.19 (1.16, 1.23) [5 673] | 1.52 (1.36, 1.69) [355] | 1.23 (1.13, 1.34) [579] | 1.06 (1.00, 1.12) [1566] | 1.21 (1.12, 1.30) [810] | 1.37 (1.24, 1.52) [398] | 1.38 (1.28, 1.50) [733] | = |
| | Concomitant ibu + para | 1.05 (0.84, 1.32) [154] | 0.91 (0.29, 2.88) [3] | 0.97 (0.45, 2.10) [7] | 0.88 (0.47, 1.66) [11] | 1.05 (0.56, 1.98) [11] | 1.12 (0.58, 2.18) [10] | 1.41 (0.98, 2.04) [51] | Reference |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Renal failure** | Ibuprofen alone | 1.09 (1.00, 1.18) [442] | 1.46 (1.12, 1.89) [59] | 0.88 (0.67, 1.16) [54] | 0.85 (0.64, 1.13) [48] | 0.86 (0.61, 1.21) [34] | 1.10 (0.78, 1.55) [33] | 1.42 (1.19, 1.71) [130] | Ibuprofen alone |
| | Paracetamol alone | 1.20 (1.14, 1.27) [1 372] | 1.31 (1.03, 1.68) [66] | 1.21 (1.02, 1.43) [142] | 1.16 (1.04, 1.29) [423] | 1.27 (1.10, 1.47) [217] | 1.44 (1.18, 1.75) [109] | 1.34 (1.15, 1.57) [182] | Paracetamol alone |
| | Concomitant ibu + para | 1.04 (0.67, 1.60) [23] | 2.35 (0.55, 10.10) [2] | 0.53 (0.07, 3.96) [1] | 0.39 (0.05, 2.91) [1] | – [0] | 1.90 (0.56, 6.45) [3] | 1.63 (0.75, 3.54) [10] | Reference |
| **Suicidal behaviour** | Ibuprofen alone | 1.40 (1.32, 1.49) [1 072] | 1.13 (0.99, 1.30) [226] | 1.19 (1.03, 1.37) [191] | 1.58 (1.33, 1.88) [135] | 1.14 (0.84, 1.54) [42] | 1.51 (1.10, 2.08) [39] | 1.71 (1.41, 2.06) [111] | = |
| | Paracetamol alone | 1.40 (1.29, 1.52) [692] | 1.10 (0.85, 1.41) [64] | 1.23 (0.98, 1.55) [78] | 1.28 (1.08, 1.51) [157] | 1.69 (1.33, 2.14) [74] | 1.83 (1.31, 2.57) [35] | 2.33 (1.84, 2.94) [77] | = |
| | Concomitant ibu + para | 1.50 (0.98, 2.31) [31] | 2.08 (0.88, 4.93) [6] | 1.43 (0.56, 3.63) [5] | 1.42 (0.51, 4.00) [4] | 0.82 (0.11, 6.03) [1] | 2.19 (0.52, 9.18) [2] | 1.36 (0.48, 3.91) [4] | Reference |
| **Overdose** | Ibuprofen alone | 1.52 (1.43, 1.62) [1 130] | 1.19 (1.04, 1.37)* [219] | 1.28 (1.11, 1.48) [201] | 1.77 (1.50, 2.08) [150] | 1.03 (0.75, 1.41) [39] | 1.62 (1.20, 2.19) [43] | 2.03 (1.71, 2.41) [137] | = |
| | Paracetamol alone | 1.42 (1.32, 1.53) [820] | 1.22 (0.96, 1.56) [71] | 1.09 (0.87, 1.37) [79] | 1.27 (1.09, 1.48) [196] | 1.85 (1.52, 2.26) [108] | 1.73 (1.28, 2.34) [44] | 2.12 (1.72, 2.63) [94] | = |
| | Concomitant ibu + para | 1.33 (0.90, 1.96) [37] | 2.00 (0.90, 4.43) [7] | 1.36 (0.58, 3.17) [6] | 1.60 (0.68, 3.77) [6] | 0.58 (0.08, 4.25) [1] | 1.51 (0.36, 6.30) [2] | 1.17 (0.46, 3.02) [5] | Reference |
| **Mortality** | Ibuprofen alone | 1.12 (1.10, 1.15) [7 265] | 1.44 (1.35, 1.54)* [948] | 1.00 (0.93, 1.07)* [850] | 0.80 (0.74, 0.86) [681] | 0.87 (0.79, 0.94)* [546] | 1.03 (0.95, 1.13) [535] | 1.31 (1.25, 1.36)* [2325] | = |
| | Paracetamol alone | 1.28 (1.26, 1.30) [28 813] | 1.95 (1.87, 2.04) [2176] | 1.18 (1.14, 1.23) [2771] | 0.95 (0.92, 0.97) [6784] | 1.08 (1.05, 1.12) [3821] | 1.27 (1.21, 1.33)* [2012] | 1.63 (1.58, 1.68) [5201] | = |
| | Concomitant ibu + para | 1.50 (1.34, 1.68) [623] | 1.78 (1.23, 2.59) [30] | 1.57 (1.16, 2.12) [47] | 0.93 (0.67, 1.28) [41] | 1.23 (0.89, 1.69) [43] | 0.86 (0.58, 1.30) [25] | 1.72 (1.45, 2.04) [226] | Reference |

** P* value <0.05 comparing the RR during current exposure with ibuprofen only or paracetamol only with the RR during current exposure of similar characteristics to concomitant paracetamol and ibuprofen (i.e. RR in same column). †Test for proportionality of RR over time after prescription, from current to past exposure, in an analysis (stratified by exposure characteristics and adjusted for age, gender and calendar year): = indicates that the RR were statistically proportional over time (*P* value of test for proportionality >0.05) and that the RR did not change despite changes in exposure; if there was a statistical interaction between RR and time, the table lists the subgroup with an increased hazard rate during current exposure. ibu, ibuprofen; para, paracetamol; RR, relative rates; [*n*], number of cases during current exposure (no prescribing of other NSAIDs or aspirin in the preceding 6 months).

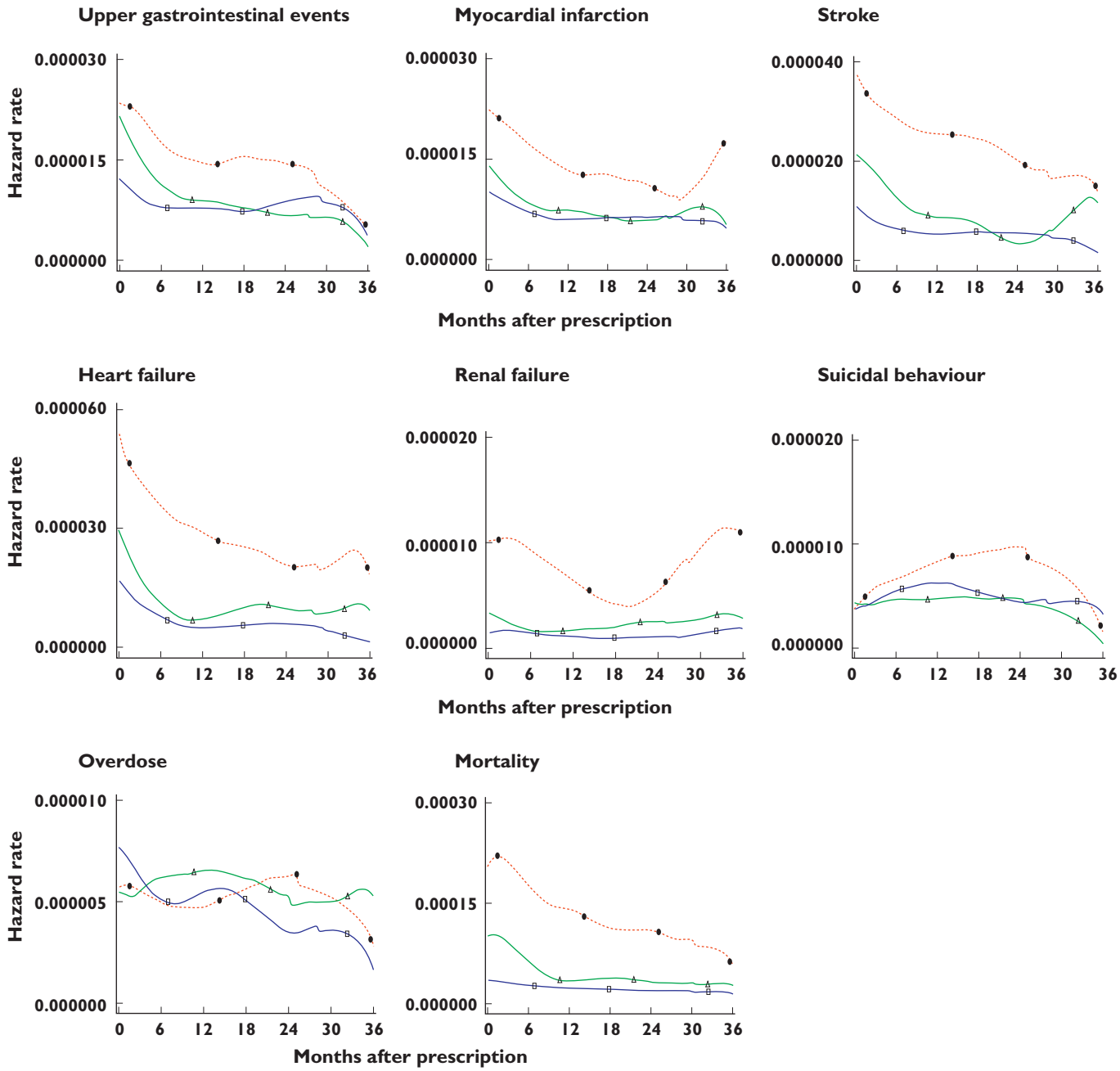


**Figure 1**

Pattern of the crude hazard rates for safety outcomes in the 36 months following an ibuprofen and/or paracetamol prescription. Concomitant paracetamol and ibuprofen (Δ), ibuprofen only (□), paracetamol only (●)

observed to be increased substantially around the time of the first NSAID prescription. This finding may be explained by protopathic bias, which occurs when a drug is inadvertently prescribed for an early manifestation of a disease that has not been diagnostically detected [22]. This bias has been described in other settings [7, 23]. For example, a study in the Netherlands found that recent starters of $\beta_2$-adrenoceptor agonists have an increased MI risk, especially patients with a history of ischaemic heart disease [23].

## *Main limitations of the study*

Patient exposure was based on prescription information rather than actual use. In addition both paracetamol and ibuprofen are available OTC. Use of OTC medications is rarely recorded by GPs and patients prescribed ibuprofen

or paracetamol as monotherapy might also be taking the other or another NSAID as an OTC. This may result in misclassification of past users and concomitant ibuprofen and paracetamol use, which would have resulted in an underestimate of any treatment effect. Because there are no data in the public domain on the actual intake of OTC medications in the population that we have studied, we were not able to quantify the extent of the misclassification of exposure and the impact on the relative rates. Another limitation is that ibuprofen and paracetamol prescribed on the same date may not necessarily be used by patients at the same time. This again is likely to have underestimated any effects of concomitant ibuprofen and paracetamol use.

As expected with an observational study, information for some of the risk factors associated with the outcomes is incomplete (e.g. details on disease severity). The pattern analysis evaluated the presence of differential effects that varied between current and past exposure. A limitation of this pattern analysis, similar to standard epidemiological analyses, is bias by time-dependent confounding (i.e. differential changes in risk factors in the comparison groups over time).

### *Overall conclusion*

There was considerable heterogeneity in the patient and exposure characteristics between groups. The 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.

## Competing interests

This study was funded by Reckitt Benckiser. The GPRD is owned by the UK Department of Health and operates within the MHRA. The GPRD is funded by the MHRA, Medical Research Council, various universities, contract research organizations and pharmaceutical companies. The Department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private–public-funded Top Institute Pharma (www.tipharma.nl) includes co-funding from universities, government, and industry, the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health. The authors also acknowledge the editorial assistance provided by Elements Communications Ltd, Westerham, Kent, UK. There are no other competing interests to declare.

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# Ibuprofen and acetaminophen kinetics when taken concurrently

*We evaluated kinetics of ibuprofen and acetaminophen taken concurrently by 20 healthy adults in a randomized crossover design. Steady-state blood levels of ibuprofen and acetaminophen were measured by gas-liquid chromatography and HPLC. There were no significant differences in any of the ibuprofen serum concentrations, but there were differences in acetaminophen serum concentrations in 5 of 19 sampling times. When bioavailability and kinetic parameters for both drugs were compared, there were no significant differences. Our data demonstrate that steady-state kinetics of ibuprofen and acetaminophen are not changed when taken concurrently.*

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*Clinical Biopharmaceutics Research Unit, The Upjohn Company*

Acetaminophen is a common over-the-counter (OTC) analgesic. The magnitude of its use exposes patients to potential drug interaction. It is generally assumed, however, because of few reports of drug interactions in the literature, that patients receiving prescription drugs may safely take acetaminophen. Studies have shown an effect on the absorption of acetaminophen by drugs that alter gastrointestinal mobility.[3, 6, 7, 9] Only with codeine are there published reports of no interaction with acetaminophen.[1, 8] Acetaminophen is also commonly used as a "rescue" drug for subjects participating in analgesic efficacy trials. When a rescue drug is taken, the kinetic evaluation of the investigational drug may be jeopardized. For example, aspirin cannot be used as a rescue drug in studies evaluating nonsteroidal, anti-inflammatory drugs because of reported kinetic interactions.[2, 5, 11–13] Since acetaminophen is used as rescue medication in many clinical efficacy-kinetic studies designed to evaluate potential new indications for nonsteroidal, anti-inflammatory drugs, the validity of the kinetic evaluation of nonsteroidal drugs once acetaminophen has been taken must be proved. Our purpose was to evaluate the kinetics of ibuprofen and acetaminophen given separately and in combination.

## Methods

Our subjects were 21 healthy adults (13 men and 8 women).* Average age of the subjects was 28 yr (19 to 42) and average weight was 72 kg (54 to 88). Before the study each subject had a complete physical examination as well as a laboratory evaluation. They had not received any medications for 30 days before the study that were known to induce or inhibit drug-metabolizing enzymes. No other medications were taken by the subjects within 7 days before

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Reprint requests to: C. Eugene Wright III, Pharm.D., Clinical Biopharmaceutics Research Unit, The Upjohn Company, 9122-243-125, 7000 Portage Rd., Kalamazoo, MI 49001.

*One subject withdrew from the study for reasons unrelated to the study.

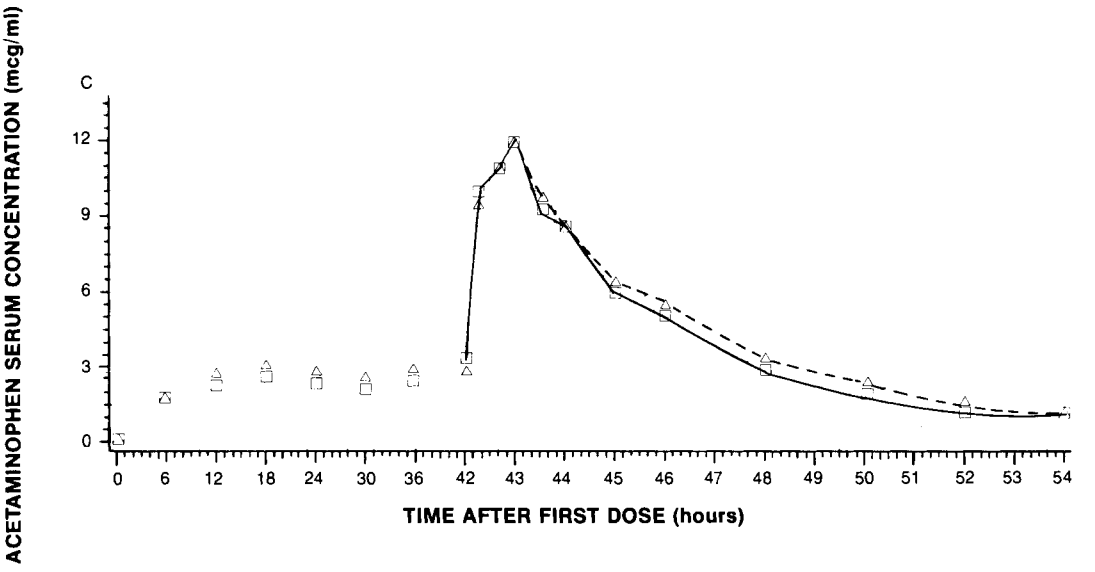


**Fig. 1.** Average acetaminophen serum concentrations for 20 subjects after 650 mg acetaminophen alone (-⊟-) and with 400 mg ibuprofen (-△-) every 6 hr.

**Table I.** *Bioavailability parameters after multiple-dose acetaminophen and ibuprofen alone and in combination*

| *Parameters* | *Acetaminophen alone* | *With ibuprofen* | *Signifi-cance* | *Ibuprofen alone* | *With acetaminophen* | *Signifi-cance* |
|---|---|---|---|---|---|---|
| $C_{max}$ (mcg/ml) | 14.2 ± 4.0 | 13.8 ± 4.3 | NS | 40.5 ± 0.8 | 42.3 ± 11.6 | NS |
| $t_{max}$ (hr) | 0.9 ± 0.5 | 0.8 ± 0.4 | NS | 1.4 ± 0.7 | 1.4 ± 0.7 | NS |
| AUC ($\mu$g × hr/ml) | 39.5 ± 12.0 | 41.6 ± 13.0 | NS | 115.0 ± 22.2 | 114.0 ± 25.1 | NS |

$C_{max}$ = average of the individual's peak concentration; $t_{max}$ = average time to reach peak concentration; AUC = average serum AUC from 0 to 6 hr after the last dose.

or during the study. None of the subjects had ever experienced a hypersensitivity reaction to ibuprofen or acetaminophen.

The drugs were taken in a randomized crossover design with a 12-day washout period between the treatments, which were given every 6 hr (1 A.M., 7 A.M., 1 P.M., and 7 P.M.) for a total of eight doses. The treatments were as follows: (1) 400 mg ibuprofen, (2) 650 mg acetaminophen, and (3) 400 mg ibuprofen and 650 mg acetaminophen together. Meals were eaten 2 hr before dosing for each dose of the multiple-dose regimen except the last dose, which was preceded by an 8-hr fast.

On day 1 subjects were confined to the clinic overnight. On day 2 subjects were confined overnight, and the confinement continued until after the 12-hr blood sample was drawn. Subjects returned to the clinic to receive medication. During each treatment blood samples were drawn from the subjects before each dose of the multiple-dose regimen. After the last dose blood samples were collected by individual venipuncture at 10 and 20 min, and at 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr after dosing. Serum was harvested from the blood samples soon after collection and was immediately frozen. Serum samples were kept frozen at −15° until assayed for ibuprofen by gas-liquid chromatography[4] and for acetaminophen by HPLC.[10]

Serum AUC between 0 and 6 hr after the last dose of the multiple-dose regimen of ibuprofen and acetaminophen was calculated by the trapezoidal rule. Total body clearance (Cl) of both drugs was calculated as dose/AUC, assuming 100% absorption. Elimination rate constant ($k_{el}$) was calculated by least-squares regression over the terminal log-linear portion of each sub-

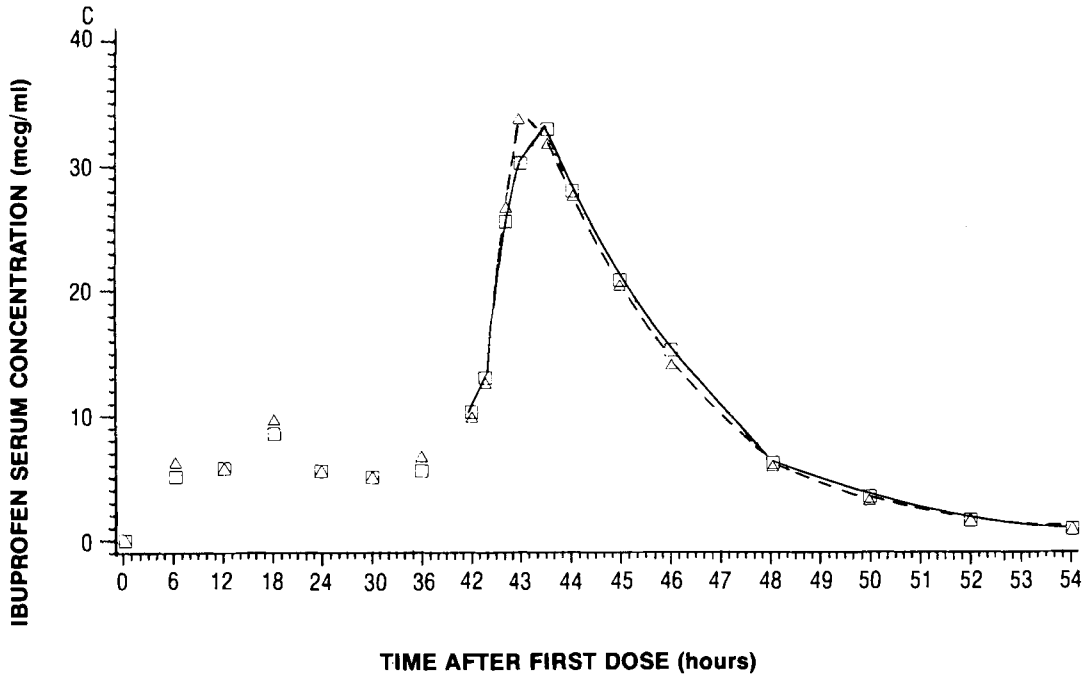


**Fig. 2.** Average ibuprofen serum concentrations for 20 subjects after 400 mg ibuprofen alone (-□-) and with 650 mg acetaminophen (-△-) every 6 hr.

**Table II.** *Kinetic parameters after multiple-dose ibuprofen and acetaminophen alone and in combination*

| *Parameters* | *Acetaminophen alone* | *With ibuprofen* | *Significance* | *Ibuprofen alone* | *With acetaminophen* | *Significance* |
|---|---|---|---|---|---|---|
| Cl (*l*/hr) | 17.9 ± 5.1 | 17.2 ± 5.5 | NS | 3.6 ± 0.7 | 3.7 ± 0.8 | NS |
| $K_{el}$ ($hr^{-1}$) | 0.22 ± 0.07 | 0.22 ± 0.05 | NS | 0.36 ± 0.06 | 0.37 ± 0.08 | NS |
| Vd (*l*) | 86.0 ± 30.9 | 85.1 ± 43.4 | NS | 10.2 ± 2.6 | 10.0 ± 1.9 | NS |
| t½ (hr)* | 3.15 | 3.15 | | 1.93 | 1.87 | |

*Harmonic mean of the elimination t½ not statistically evaluated.

ject's serum level curve after the last dose. The $k_{el}$ value was then used in the calculation of the apparent volume of distribution ($Vd = Cl/k_{el}$) and the elimination t½ ($t½ = 0.693/k_{el}$). Serum levels of ibuprofen and acetaminophen and the derived bioavailability and kinetic parameters were statistically compared by a mixed-effects analysis-of-variance model with treatment and group as the fixed effect and subject within group as a random effect.

## Results

Steady-state serum levels of acetaminophen were achieved after 12 hr of initiating the multiple-dose regimen as indicated by the acetaminophen concentrations found in the predose blood samples in Fig. 1. This is consistent with the approximate 3 hr acetaminophen elimination t½. There were significant differences in acetaminophen levels at only 5 of 19 sampling times during the multiple-dose regimen (0 to 42 hr) at 12, 18, and 24 hr and after the last dose at 8 (50) and 10 (52) hr.

Ibuprofen serum concentrations reached steady-state levels after 6 hr of multiple dosing, which is consistent with an approximate 2-hr elimination t½. There were no significant differences at any time between the concentrations

resulting from ibuprofen alone and ibuprofen with acetaminophen. The mean ibuprofen serum concentration–time values for both treatments are shown in Fig. 2. There were no significant differences in the average of the individual peak concentrations, average time to reach the peak concentration, and serum AUC from 0 to 6 hr after the last acetaminophen dose when taken alone or in combination with ibuprofen. Bioavailability of ibuprofen also did not significantly change when it was taken with acetaminophen. Values for the bioavailability of ibuprofen and acetaminophen are reported in Table I. Table II lists acetaminophen and ibuprofen kinetics resulting from dosing with each drug individually as well as in combination. There were no significant differences in Cl, $k_{el}$, or apparent Vd of acetaminophen or ibuprofen.

## Discussion

Our data demonstrate that steady-state kinetics of acetaminophen and ibuprofen are not changed when these drugs are taken together. That the combination of both drugs did not affect the bioavailability of either drug is shown by the absence of difference in parameters that reflect the rate and extent of absorption. Vd, Cl, and $k_{el}$ were the same for each drug regardless of the treatment mode. Blood-level profiles were essentially indistinguishable for both.

Our study establishes that acetaminophen may be recommended as an OTC analgesic for patients with rheumatoid arthritis who are also taking ibuprofen. In contrast, because aspirin markedly lowers blood (serum and plasma) levels of ibuprofen,[2] its use as an analgesic for these patients can be questioned on kinetic grounds. It should be kept in mind that clinical significance of the ibuprofen-aspirin interaction has not been proved but that there is a potential for alteration in the efficacy of these drugs. The absence of any kinetic interaction and the much lower incidence of gastrointestinal side effects makes acetaminophen the most appropriate choice as an OTC analgesic for patients taking ibuprofen.

Our results are also applicable to clinical research with ibuprofen. Ibuprofen kinetics can be evaluated in patients with rheumatoid arthritis or osteoarthritis even after acetaminophen is taken as a rescue measure. This is especially important in multiple-dose studies designed to evaluate ibuprofen kinetics in arthritic patients.

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## 2.2.2 Pantoprazole - further submission 1 of 1.

[redacted]

11 May 2011

The Secretary
Medicines and Poisons Scheduling Secretariat (MDP 88)
Department of Health and Ageing
GPO Box 9848
CANBERRA ACT 2600
Australia

Dear Secretary

**Re: February 2011 meeting of the Advisory Committee on Medicines Scheduling (ACMS) – ACMS#2**
**Agenda item 2.2.2; PANTOPRAZOLE – proposal to create a new entry for pantoprazole in Appendix H**
**Comment from [redacted] on the delegates' reason for interim decisions**

[redacted] herewith makes a post-meeting comment in relation to the **February 2011 meeting of the Advisory Committee on Medicines Scheduling (ACMS)** with reference to the Expert Advisory Committee Discussion and resultant Delegate's interim decision regarding the application for pantoprazole [redacted] to be included in Appendix H.

[redacted] submits that [redacted] is a suitable candidate for Appendix H listing.

- The original application has addressed each of the matters for consideration of a product for Appendix H listing, as specified in the NCCTG Guidelines for brand advertising of substances included in Schedule 3 of the Standard for Uniform Scheduling of Drugs and Poisons.
- The Evaluator supports Appendix H listing, has agreed that the arguments presented are reasonable and that the data provided supports a public health benefit.
- The Evaluator has identified no negative impact of advertising this product.
- The issues raised by some members of the ACMS, who were not in favor of Appendix H Listing, are more relevant to the *scheduling* of pantoprazole and have minimal bearing on the current application which seeks only to *amend the appendices*.
- None of the February 2011 pre-meeting submissions opposed the Appendix H listing.
- The delegate, by referring the proposal to the ACMS, has intimated that the current scheduling (ie no appendix H listing) may not be appropriate.



[redacted]

[redacted]

The delegate's interim decision is aligned with the recommendations of the ACMS. We would therefore like to address each of the points raised by the ACMS in their discussion in order that the delegate may further consider them prior to making a final decision.

*Issues raised relating to the benefit of advertising of PPIs*

[redacted] application asserted that the advertising of [redacted] would meet the primary purposes for which such advertising is intended; namely:

- Protection of public health by identifying customers whose condition warrants referral to their GP, and who may otherwise have not sought such advice and thus remained unidentified.
- Improvement in health outcomes by checking that consumers with frequent, moderate to severe heartburn are being offered the most appropriate, evidence-based treatment for their condition.

Having accepted this argument, the Evaluator recommended that the application should be approved. **None of the Members disputed this argument or the Evaluator's conclusions**.

*"A Member asserted that if pantoprazole was included in Appendix H, a consistent approach should be maintained for all PPIs to ensure awareness of multiple treatments."*

- As a general principle, [redacted] agrees that a consistent approach should be taken into account when determining the merits of applications. Previously, applications for Appendix H listing have been rejected on the grounds that it is beneficial to first have relevant in-market use. In this respect, we submit that a class approach would not be appropriate at this time because [redacted] PPI in Australia with significant in-market experience (which is now in excess of 2.5 years). Moreover, [redacted] is the only PPI listed in Schedule 3 that has published data demonstrating appropriate supply in the Australian setting.[1]

- Notwithstanding the above, scheduling decisions and entries into the SUSMP are product based, not class based. As was stated in our pre-meeting submission recent data have been published that support the presence of a true metabolic drug-drug interaction between clopidogrel and omperazole.[2] This interaction is not a class effect. Thus, when making scheduling decisions the safety profiles of the individual active ingredients, rather than PPIs as a class, should be taken into consideration.

*"Another Member contended however that the aim of product advertising was to increase product awareness (and resultant market share), not to improve community awareness of a disease and all its available treatments. The Member noted that a television campaign aimed at increasing the awareness of GORD currently exists and an Appendix H listing for PPIs would not provide additional benefit to the public's awareness of available forms of treatment."*

- [redacted] is aware of the television campaign being sponsored by the manufacturer of a prescription PPI product. The television campaign is aimed at directing consumers to their GP for assessment and (potentially) a prescription. This campaign therefore does not improve community awareness of Pharmacy based treatment options. Moreover, as is evidenced in the Gut Foundation report, there is a high degree of reluctance to consults a GP for heartburn amongst Australian consumers.[3]
- As has been set out in [redacted] application [redacted] contends that the ability to advertise to consumers will provide a number of positive benefits to the community.
    - It provides a means of raising awareness of the Pharmacist's ability to provide advice and effective treatment for heartburn.
    - It aids in guiding more heartburn sufferers into the Pharmacy.
    - It promotes a better use of professional expertise.
    - In conjunction with the Pharmacist educational materials, it facilitates early identification of atypical symptoms or "red flag" symptoms that require medical referral, leading in turn to more timely medical consultation with resultant cost savings, and better health outcomes including improved work productivity.
- [redacted] asserts that Appendix H listing will improve community awareness of frequent heartburn and all of its available treatment options because advertising will guide people to the Pharmacy where the Pharmacist can assess the severity and frequency of their symptoms and offer the most appropriate treatment option (be it an antacid, an $H_2$RA, a PPI or referral to a GP).

*Issues raised relating to diagnosis*

[redacted] application sought only to list [redacted] in Appendix H. Pantoprazole has been listed as a Schedule 3 medicine since June 2005, albeit not having been launched into the market until October 2008. [redacted] application provides substantive safety data including in-market OTC use data from Australia and other markets.

The Evaluator has agreed that these data are convincing, and the safety of self-management, with the advice of a Pharmacist, has been recognised by the rescheduling decision taken by the NDPSC in 2005. It follows that it is already established that "*The consumer can identify the ailments or symptoms that may be treated by the medicine but counselling and verification by a pharmacist is required before use. Pharmacist-consumer dialogue is necessary to reinforce and/or expand on aspects of the safe use of the medicine.*" **None of the Members disputed the current scheduling status of** [redacted].

Each of the issues raised by various members (as detailed below) is relevant to the Scheduling of pantoprazole and has minimal, if any, bearing on the current application for an amendment to the Appendices. Additional comments are made below to further clarify certain points.

[redacted]

*"A Member asserted that GORD requires diagnosis by appropriately qualified practitioners (i.e. pharmacists)."*

- [redacted] is not indicated for the management of GORD. Rather, like all other OTC products in this category is it indicated for the symptomatic relief of symptoms associated with GORD, such as heartburn and acid regurgitation.

*"The Member also stated that unlike H2RAs, there was a risk that pantoprazole could mask symptoms of more serious disorders and advice was required before a treatment was selected."*

- The risk of masking is a factor that is considered in scheduling amendments not amendments to the appendices. This issue has therefore been adequately addressed by the current scheduling status of the product.
- Notwithstanding that, as was presented in our submission, consensus guidelines on the use of OTC PPIs prepared by an international group of experts, of whom 3 are Australian based, conclude that **"It is not anticipated that OTC PPIs, used in this recommended fashion, will lead to any greater problems than with the current OTC use of less effective agents."**[4]
- We disagree with the statement made by the Member and submit that any risk of masking/hiding an underlying condition requiring medical attention and supervision with OTC pantoprazole is similar to that of all other approved heartburn OTC medications. We are aware of no published data to counter this contention.

*It was asserted that advertising of pantoprazole would transfer the responsibility of diagnosis onto the consumer which may inappropriately increase pressure on the pharmacist for supply of this product.*

- The issue of Pharmacy workloads has been discussed in relation to prior submissions. The overall aim of advertising is to prompt consumers to seek Pharmacist advice. If increased pressure on the Pharmacist for supply of this product was a concern, it would surely have been raised as an issue by key Pharmacy groups. Support for the proposal from the Pharmaceutical Society of Australia would suggest that the pharmacy profession itself does not have this concern in this particular instance.
- The current submission provides a published Australian audit of Pharmacy practice, which demonstrated that Pharmacists were able to determine which customers had frequent heartburn, appropriately recommend treatment, and appropriately identify the presence of "red flag" symptoms and refer customers with severe symptoms to their general medical practitioners.

[redacted]

- Importantly, despite the fact that [redacted] was a suitable choice for 77% of patients, the Pharmacists recommended [redacted] to only 106 (69%) of patients and only 89 (58%) of patients actually purchased the product. This demonstrates that (a) Pharmacists are exercising their own clinical judgement in determining the appropriateness of use of this product and (b) that consumers are heeding that advice (demand for purchase did not outweigh recommendation rates). As has been summarised in the published paper consumers are exercising caution, listening to the Pharmacist and not unrealistically demanding a product which may not be clinically justified in their case.

*"Members also noted that PPI efficacy relies on consistent use over a longer period of time."* and *"A Member asserted that advertising may inadvertently reinforce inaccurate consumer expectations that PPIs, like some other GORD treatments, may be used as a "quick fix" and would not require adherence to treatment."*

- The aim of Appendix H listing of pantoprazole is to increase awareness and drive more heartburn sufferers into the pharmacy. This in turn 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.
- Any contention that the Pharmacist would not be able to adequately explain the use of the product to the consumer and/or that the consumer would not understand that the product is not intended for immediate relief or that it should be taken for a minimum of 7 days is countered by the following:
    - A CMI and package leaflet have already been approved by the TGA; they provide clear instructions on the use of [redacted], including what the product is used for, how long it should be used and what to do if sufficient symptom relief is not achieved.
    - It is anticipated that the Pharmacist will also provide a verbal summary on how to use the product which will further reinforce the CMI and the package leaflet.
    - Consumer label comprehension, undertaken, as part of the pharmacy audit did not highlight any cause for concern with regards to these instructions.[1]
    - We have provided examples of advertising from Europe; these contain nothing to suggest that the product would be portrayed, inadvertently or otherwise, in any manner that conflicts with the approved OTC Prescribing Information.
    - In the application, [redacted] have made an undertaking the requested addition of pantoprazole 20 mg to Appendix H will not result in the advertising of goods for an indication other than those included in the Australian Register of Therapeutic Goods. [redacted] is a reputable [redacted]

[redacted], and is cognisant of the constraints placed upon advertising a Schedule 3 product including the penalties imposable for breach of Section 22(5) of the Therapeutic Goods Act 1989.

*Issues raised relating to factors other than those outlined in the SPF for inclusion of substances in Appendix H*

The SPF states the following with regard to how matters relating to Appendix H should be considered.

> ***Appendix H – Schedule 3 medicines permitted to be advertised***
>
> ***The decision-maker should make their determination after taking into account matters set out in the NCCTG Guidelines for brand advertising of substances included in Schedule 3 of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) (November 2000). (Note: A review of advertising arrangements for therapeutic goods is under consideration. Until this review has been finalised, Appendix H will be retained in the Poisons Standard.)***

At the present time, Appendix H is still retained with the Poisons Standard. Whilst [redacted] concurs that the title of the reference document is a "guideline", its instruction is neither ambiguous (cf: *In making a decision, as to whether a substance included in Schedule 3 of the SUSDP may be advertised to the public, the NDPSC will consider the following matters*) nor does it provide scope for the need to consider "other factors". [redacted] submits that each of the matters listed in the above guideline has been adequately addressed in the current application. None of the Members publicly disputed that these matters have been adequately addressed and one Member "*noted that pantoprazole may appear to be a suitable candidate for Appendix H listing according to these factors.*"

[redacted] is concerned therefore that other Members felt that an amendment to Appendix H should be subject to consideration of other additional factors. The nature of these "other factors" has not been disclosed making it impossible for [redacted] to adequately address them.

*Issues raised in the pre-meeting public comments*

All of the pre-meeting public comments were supportive of the proposal to list [redacted] in Appendix H. However, we feel that the following potential issue, raised in one letter, warrants comment:

> *"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] asserts that the scenario of a medicine being simultaneously available in the OTC and the prescription setting is neither new nor unique to the category of PPIs. Such

[redacted]

a consideration has not previously been raised as an issue in terms of changes to scheduling and/or Appendix H listings. Moreover it is common practice for products with the same active ingredient to be marketed under distinct, but related, brand names in the OTC and prescription settings.

- **Voltaren Rapid 25** (diclofenac) is a highly relevant example of a **Schedule 3** product that is able to be advertised (**listed in Appendix H**) despite having a prescription counterpart with a similar name, **Voltaren Rapid 50**. Interestingly, **Voltaren Rapid 25** and **Voltaren Rapid 50** both carry the same indication.
- Similarly, the $H_2$RA ranitidine is available and advertisable in the OTC setting — **Zantac Relief** is unscheduled and **Zantac Extra Strength** is Schedule 2 —while **Zantac** is available only on prescription. The prescription only **Zantac** product is available in larger pack sizes.

[redacted] submits that the Schedule 3 brand name for pantoprazole [redacted] is sufficiently distinct to its prescription counterpart [redacted]. The distinction between the Schedule 3 and Schedule 4 brand name is greater than that of **Voltaren Rapid** and comparable to that of **Zantac** and is therefore not a determining factor in the suitability of pantoprazole for Appendix H listing.

In summary

[redacted] submits that there has been an overall positive response to the current application to include [redacted] in Appendix H. The data provided in our application demonstrate the potential public health benefit of this change.
Currently many frequent heartburn sufferers are taking products purchased in general sales outlets and not seeking healthcare professional advice. Direct to consumer advertising of [redacted] will promote awareness of the Pharmacist as a source of advice and of a Pharmacy Only medicine specifically for frequent moderate to severe heartburn. In doing so, it will help drive consumers into the pharmacy, where they can obtain appropriate counselling and GP referral if warranted. This opportunity for GP referral is missed amongst those consumers who do not seek Pharmacist advice for their heartburn. Pharmacist intervention would ensure:

- Protection of public health by identifying customers with red flag symptoms and referring them to their GP for further investigation, such patients would otherwise be overlooked.
- Improvement in health outcomes by ensuring that consumers with heartburn are offered the most appropriate, evidence-based, treatment for their condition.

The proposal has adequately addressed all of the matters for consideration of a product for Appendix H listing, as specified in the NCCTG Guidelines for brand advertising of substances included in Schedule 3.
The proposal has been supported by the external Evaluator, who recommended:

[redacted]

*"It is recommended that the application for an entry for pantoprazole (when supplied in accordance with the existing entry in Schedule 3) in Appendix H of the SUSDP (Schedule 3 Poisons Permitted to be Advertised) should be APPROVED."*

The proposal has been supported in all of the public submissions received during the consultation phase.

Whilst the ACMS has raised some factors and therefore erred on the side of caution in its recommendation, as has been demonstrated above, many of these factors are either not relevant to an appendix H listing application (a fact acknowledged by a member of the ACMS) or have been adequately addressed by the data provided.

**It is based on the above that we ask the delegate to vary the interim decision and decide that pantoprazole 20 mg, when supplied in accordance with the existing entry in Schedule 3, be approved for inclusion in Appendix H of the SUSDP.**

I trust that the above is of value. Should you require any further information, please do not hesitate to contact me on telephone [redacted] or email [redacted].

Yours faithfully,

[redacted]

[redacted]

[redacted]

Reference List


(1) Bell J, Katelaris P, Krassas G. An Australian pharmacy audit of the management of heartburn and the role of over-the-counter proton pump inhibitors. *Aust Pharmacist* 2010;29(6):526-8.

(2) Angiolillo DJ, Gibson CM, Cheng S et al. Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther* 2011 January;89(1):65-74.

(3) Access Economics Pty Ltd. Gut Instincts: the economic impact of GORD and PUD. 2007 May 3.

(4) Haag S, Andrews JM, Katelaris PH et al. Management of reflux symptoms with over-the-counter proton pump inhibitors: issues and proposed guidelines. *Digestion* 2009;80(4):226-34.