Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Cyclizine lactate

Proprietary Product Name: Valoid

Sponsor: Link Medical Products Pty Ltd

January 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	13 June 2012
Active ingredient:	Cyclizine lactate
Product Name:	Valoid
Sponsor's Name and address:	Link Medical Products Pty Ltd 5 Apollo St Warriewood NSW 2102
Dose form:	Injection solution
Strength:	50 mg/1 mL
Container:	Ampoule
Pack size:	5 ampoules/carton
Approved Therapeutic use:	For the prevention of nausea and vomiting in the post operative period.
Route of administration:	Intravenous (IV) injection
Dosage:	50 mg up to three times daily
ARTG Number:	180894

Product background

This AusPAR describes the application by Link Medical Products Pty Ltd to register Valoid injection containing cyclizine lactate 50 mg/1 mL as a new chemical entity (NCE).

Cyclizine is a piperizine-derivative histamine H_1 receptor antagonist with anticholinergic activity. It has been used internationally to treat nausea and vomiting due to various causes and in various settings for more than 50 years but has never been registered in Australia[1]. The anti-emetic mechanism of action of cyclizine is not fully understood but is thought to be *via* anti-muscarinic and anti-histamine effects at the chemoreceptor trigger zone of the vomiting centre in the midbrain; and possibly also involves antispasmodic effects on intestinal smooth muscle.

The sponsor initially proposed the following indications for cyclizine lactate:

- the treatment of nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period
- pre-operative use in patients undergoing emergency surgery to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia

The proposed dose was 50 mg intramuscularly (IM) or intravenously (IV) up to three times daily (tid). The sponsor's request to include Cycline-Link as an additional trade name after the submission was accepted for evaluation was not considered as part of this submission.

[1] MIGRAL®, an [oral] combination product containing cyclizine, ergotamine and caffeine, was once registered in Australia but registration has since been cancelled.

Published references referred to in this AusPAR have been listed at the end of this AusPAR (under *References*).

Regulatory status

The product Valoid received initial ARTG Registration on 19 June 2012.

Valoid injection 50 mg/mL has been approved in the UK since 1985 and in Ireland since 1979. Injections containing 50 mg/mL cyclizine lactate from other sponsors are available in New Zealand and were available in Canada (first marketed in 1954) and the USA (1990) but have since been discontinued.

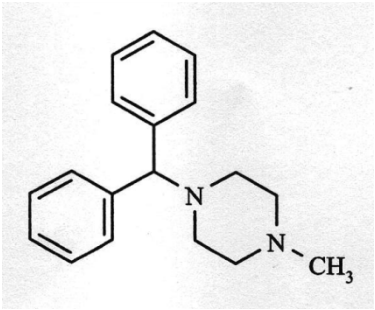
Product information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Cyclizine has the following structure:



It contains no chiral centres, and is not known to exhibit polymorphism. It is practically insoluble in water, but is readily soluble as the lactate salt at the pH of the injection (3.5). The chemical formula of cyclizine is $C_{18}H_{22}N_2$ (molecular weight 266); that of cyclizine lactate is $C_{21}H_{28}N_2O_3$ (molecular weight 356.46).

The drug substance complies with the British Pharmacopiea (BP) monograph for *cyclizine*, with the addition of a gas chromatography (GC) test for related substances analogous to that described in the BP/European Pharmacopiea (Ph. Eur.) monograph for *cyclizine hydrochloride*. Appropriate limits are applied to N- methylpiperazine (0.5%), benzhydrol (0.5%) and any unspecified impurity (0.10%).

Matters raised by TGA in relation to the manufacture of the drug substance were resolved satisfactorily.

Drug product

Cyclizine lactate is defined as the 1:1 salt of cyclizine and lactic acid. The product is labelled in terms of the content of cyclizine lactate (50 mg cyclizine lactate is equivalent to 37.4 mg cyclizine base).

The excipients used in the manufacture of the drug product comply with pharmacopoeial standards. They are conventional for use in the manufacture of parenteral products and were found to be acceptable. None is derived from animals or genetically modified organisms.

The manufacturing methods utilised are conventional processes commonly used to produce parenteral drug products. No reprocessing procedures are proposed at this point in time.

The quality evaluator initially considered that approval of this submission could not be recommended until a suitable method for monitoring the finished product had been developed and appropriate stability data using that method were generated. This subsequently occurred.

The proposed shelf life of 4 years below 25°C was considered acceptable.

Biopharmaceutics

Biopharmaceutic data are not required for the IV route of administration. No data were submitted on the bioavailability of the injection when administered by the intramuscular (IM) route.

Advisory committee considerations

Quality aspects were considered at the 140th (2011/5) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Precription Medicines (ACPM), held August 2011. The PSC endorsed all the questions raised by the TGA in relation to quality and pharmaceutic aspects of the submission and did not require the submission to be re-presented to the subcommittee.

Quality summary and conclusions

There were no biopharmaceutic data to support IM administration and therefore approval of Valoid by this route was not recommended.

III. Nonclinical findings

Introduction

Although cyclizine has a very long history of clinical use, the nonclinical animal studies cited in this dossier (submitted as a literature-based submission) are not as comprehensive or scientifically robust as would be expected to support the registration of a NCE, because of their age (preceding regulatory guidelines), design, lack of good laboratory practice (GLP)-compliance, and minimal coverage of nonclinical issues.

The quality of the documents supplied was variable and at times problematic with regard to print quality (illegibility of some figures and tables) and on some occasions, language, where foreign language reports were provided without accompanying English translations (these were subsequently provided on request). Some documents referenced as nonclinical studies would have been more suited to the clinical section of the dossier and vice versa. On one occasion an abstract from the proceedings journal of a conference was cited as a source, when using the full published report would have been more appropriate and useful.

On a positive note, the inclusion of an organisational table, which listed the cited reports in the order of those used to substantiate a particular section of the nonclinical submission aided in understanding the rationale for their inclusion in the dossier.

Pharmacodynamics

Primary pharmacodynamics

Cyclizine is a piperazine-derivative histamine H_1 receptor antagonist, also believed to exert antimuscarinic actions. These antimuscarinic actions combined with the antihistaminic effects of cyclizine may be partially responsible for its central antiemetic effects by an action on the vestibular system and the chemoreceptor trigger zone.

There were little data that specifically addressed the primary pharmacodynamic effects of cyclizine relevant to the proposed indication. However, the data published by Dent *et al*., 1954 did show an inhibitory effect by cyclizine on an experimental model of emesis (42% reduction in the incidence of vomiting in dogs). Cyclizine was also shown to afford protection against histamine shock and severe bronchoconstriction in guinea pigs exposed to nebulised histamine (Norton *et al*., 1954). There were also other observations related to the antihistaminic properties of cyclizine (such as inhibition of histamine-induced changes to blood pressure in anaesthetised cats and spasms in isolated guinea pig ileum). However, and

perhaps reflecting the age of these reports (approximately 60 years), the studies were not well designed as part of a human pharmaceutical development regimen, because little information was provided on dose-dependency and specificity of actions; as well, there was a lack of quantifiable measures of the actions of cyclizine (that is, no 50% inhibitory concentration (IC_{50}) data were provided for any of the animal models). These deficits can be put into context, with the far less rigorous requirements for pharmacological and mechanistic supporting studies at the time that this medicine was developed, followed by the extensive history of clinical use of cyclizine for the proposed or related indications. The absence of sufficient nonclinical evidence of efficacy for the proposed indications will require adequate clinical evidence of efficacy.

Secondary pharmacodynamics

Very little data were provided that explored the secondary pharmacodynamic characteristics of cyclizine. In the one study cited, cyclizine was reported to have no effects on acetylcholine-induced changes to blood pressure, or on noradrenergic and sympathetic nervous system processes. Cyclizine reduced serotonin-induced changes to blood pressure in cats. Cyclizine was also reported to exert a local anaesthetic effect based on its ability to reduce responsiveness to painful stimuli in guinea pigs. The antimuscarinic actions of cyclizine were evident from data that showed an attenuation of changes to blood pressure that resulted following stimulation of preganglionic fibres of the vagus in anaesthetised cats (although acetylcholine-induced changes to blood pressure were not affected by cyclizine). As the source of information describing these secondary effects came from one standalone reference, it is difficult to make any comments on the reliability and reproducibility of these observations and whether they have any implications for the use of cyclizine as an antiemetic. Also further elaboration on the reported effects of cyclizine on serotonin-mediated actions (that is, serotonin-induced reductions to blood pressure) might have been useful, as it may have provides further clarification about its antiemetic mechanism of action.

Safety pharmacology

The sponsor did not undertake any formal safety pharmacology studies. Because most of the studies provided were published prior to the 1990s, they were not GLP-compliant.

The battery of safety pharmacology investigations covered the central nervous system (CNS) and cardiovascular system (CVS) only. Minimal data concerning the safety of cyclizine on the CVS were confined to two earlier reports that provided information on the effects of cyclizine on blood pressure (cats, *in vivo*) and heart rate (guinea pigs, *in vitro*), suggesting a depressant effect. No data (including data on potential effects on the electrocardiograph (ECG) and human ether-à-go-go-related gene (hERG) ion channel) were provided to give insight into potential conductance abnormalities that might arise with cyclizine. The latter safety studies are considered integral by current regulatory standards, particularly in view of the reported local anaesthetic effects of cyclizine. Safety data concerning the CNS came from only one study, which reported decreased spontaneous motor activity at 5 mg/kg by intraperitoneal (IP) injection and increased activity at 20 mg/kg IP. No effect on conditioned responses was observed when rats were given cyclizine (10 and 30 mg/kg IP). Separate reference was made to a study that reported hyperactivity in mice given cyclizine and variable locomotor interactions with opioid substances, though the significance of this to safety was not clear.

Several studies associated repeat dose (2-8 weeks) oral (PO) cyclizine with pancreatic beta islet cell damage and alterations of glucose (plasma) and insulin (plasma; beta cells *in vitro*). These effects were seen at ≥75 mg/kg/day, and one study determined a no observed effect level (NOEL) of 40 mg/kg/day PO. There were no systemic exposure data to compare with anticipated clinical exposures, limiting any extrapolation for human risk assessment[2]. In a

[2] A rough estimate of safety margin may be obtained by comparing relative doses expressed as mg/m^2 (although the administration routes differ). Thus, the 75 mg/kg dose in rats (450 mg/m^2) is approximately 4.5x a clinical dose of 50 mg tid in a 50 kg individual (99 mg/m^2). The NOEL (40 mg/kg) is *ca* 2.4x a 50 mg tid clinical dose.

request for information from the TGA, the sponsor was asked to provide evidence that these effects do not pose safety concerns for humans. In response, the sponsor referred to the significantly higher doses used in these animal studies (75 mg/kg/day) compared with the expected maximum human dose (150 mg) and the fact that these observations was associated with repeated dose exposure (2–8 weeks) compared with the proposed (considerably shorter term) use in humans (limited to peri-operative use). The sponsor also argued that concentrations of cyclizine that inhibited insulin secretion *in vitro* were equivalent to 3 μg/mL, whereas a bolus injection of 25 mg cyclizine given to healthy volunteers achieved peak plasma levels less than 100 ng/mL (30 times less), which subsequently fell to less than 3 ng/mL after 24 h. (By extrapolation, a 50 mg bolus injection may produce peak levels of up to 200 ng/mL, approximately 15 times less). The margin following repeated clinical dosing (up to 3 times a day) is unclear. In view of the proposed indication (use of cyclizine to treat short term instances of nausea and vomiting post- and/or pre-operatively; 50 mg/mL up to 3 times a day), the level and/or duration of exposure to cyclizine might not approach that eliciting potential/actual islet cell damage. Data from a Periodic Safety Update Report (PSUR) for cyclizine from April 1996 to January 2010 submitted did not signal any indication of a risk of diabetes in humans.

No information was provided on gastrointestinal (GI), renal or respiratory effects of cyclizine.

Pharmacodynamic interactions

Cyclizine exerted mild antinociceptive actions and also enhanced those of pentazocine and morphine in rats and mice[3]. The duration of antinociception was enhanced in an additive manner and was also observed with other H_1 antihistaminic drugs (for example, diphenhydramine and chlorpheniramine), which likely reflects a general involvement of histamine in central pain pathways unrelated to cyclizine itself. This may also explain the number of clinical reports that described cases of combined cyclizine and opioid abuse.

Given that the sponsors are seeking to register cyclizine for the treatment of nausea and vomiting caused by *narcotic analgesics* and general anaesthetics in the post-operative period, it may highlight the need for greater information on the interaction between opioids and cyclizine to assess any potential clinical relevance.

As a further note on opiate interactions, the PI also specified that cyclizine (as Valoid) enhances the soporific effects of pethidine, although this may refer to clinical evidence that was not referenced in the nonclinical submission.

Pharmacokinetics and relative exposure

Pharmacokinetic data are based on earlier studies with detection techniques that may lack the sensitivity of current methods (no details of Methods of Analysis were provided).

Pharmacokinetic data were very limited. There were no plasma kinetic data for the test species used in the toxicity studies. Distribution studies in rats indicated cyclizine binding to rat lung, and other tissues (lung > spleen > liver > kidney > brain > heart > muscle > plasma); plasma protein binding in rats was 59% or 76%, depending on the study. Metabolic pathways were explored by analysis of dog (greyhound) urine. Demethylation produces the major metabolite in this species, norcyclizine (M1; excreted unconjugated); also detected were four monohydroxylated compounds (M2-M5; excreted as Phase II conjugates), and four basic metabolites. Other metabolic pathways in greyhounds included N_1-dealkylation of cyclizine and the basic metabolites to form neutral[4] and phenolic Phase I metabolites containing the diphenyl-methane/methylene substructures, which are excreted as Phase II conjugates.

Cyclizine was extensively metabolised in humans, where norcyclizine was also the major urinary metabolite (although it was not always detected in serum). Following a single bolus dose of cyclizine 25 mg IV, the mean area under the plasma concentration time curve from

[3] This was not observed in all studies (for example, Pendse and Madan, 1969).
[4] Diphenylmethane (M1), benzophenone (M2), benzhydrol (M3).

time zero to infinity ($AUC_{0-\infty}$) was 273 ng.h/mL, volume of distribution 16.5 L/kg, elimination half life (t½) 13.5 h, and total clearance 0.87 L/h/kg.

In vitro assays provided some evidence for inhibition of monoamine oxidase (MAO) in mice, and cytochrome (CYP) 2D6/2C9 and sulfotransferase activities in human liver. There was variable inhibition of MAO, especially deamination of benzylamine (a selective MAO-B substrate, IC_{50} 13.5 μM). In human liver microsomes (extensive metabolisers), cyclizine showed concentration-dependent inhibition of CYP2D6 (IC_{20} 12 μM, IC_{50} 109 μM) and CYP2C9 (IC_{20} 85 μM), while in human liver homogenates cyclizine inhibited estrone sulfotransferase (IC_{50} 0.44 μM).

The clinical peak plasma concentration (C_{max}) of cyclizine in persons receiving the maximum recommended human dose (MRHD; 50 mg IV or IM up to 3 times daily) is not known, but could be in the region of 150 ng/mL (0.56 μM) from a single 50 mg injection. This suggests that potential CYP interactions are unlikely at therapeutic concentrations; the finding with liver steroid sulfotransferase may be clinically relevant.

There were no toxicokinetic measurements from any of the animal studies to compare with anticipated clinical exposure at the MRHD.

Toxicology

Acute toxicity

Acute toxicity data were provided from a study and with only one animal model (albino CF-1 mouse strain), which listed 50% lethal dose (LD_{50}) values of cyclizine when administered IP and PO. The LD_{50} values for IP administration were in the modest range (69–82 mg/kg), whereas the values derived for PO administration were approximately double (165 mg/kg).

Repeat dose toxicity

Repeat-dose toxicity was assessed in a single study using male CF rats that received dietary cyclizine at four different concentrations (doses: 0, 15, 26, 59 and 142 mg/kg/day) for a period of 12 weeks and effects on growth and blood count profiles were assessed at the end of treatment. At the highest dose, body weight gain was significantly reduced (no effect at lower doses). There were no apparent effects on blood chemistry or haematology. Post mortem analyses revealed changes to liver morphology as well as evidence of pulmonary oedema; otherwise no other assessments were conducted to assess changes. These studies preceded observations concerning the effects of cyclizine on pancreatic islet cells, and there was no confirmatory gross pathology of pancreatic tissue or measurement of blood sugar to ascertain a potential diabetogenic effect of cyclizine (as described in *Safety Pharmacology*, above).

Genotoxicity and carcinogenicity

With regard to genotoxicity, only one study was provided, exploring the possible mutagenicity of cyclizine in a bacterial system only (five strains of *Salmonella Typhimurium* were tested). The main finding from this study was that cyclizine (1000 μg/plate) on its own, and in the presence of metabolic activation, did not induce significant numbers of mutants. Cyclizine, when reacted with acidified nitrite to promote nitrosation, did however induce revertant mutants in two of the bacterial strains tested. Because the possibility of nitrosation is highest in the acidic gastric environment, it was argued that because it is to be administered parenterally cyclizine is unlikely to pose a significant risk of forming a potentially mutagenic nitrosated species. No cytotoxicity was observed at the maximal concentration used in this assay (1 mg/plate), which is considered low by current regulatory guideline standards (5 mg/plate is the stipulated maximum concentration), and the assay validity is therefore uncertain.

There was no further assessment of the genotoxic potential for cyclizine as would be expected under current nonclinical guidelines. The genotoxic potential of cyclizine has not been adequately investigated.

Scant information was provided by the sponsor on the carcinogenicity of cyclizine. Reference was made to one animal study that merely listed cyclizine among the range of substances fed to rats in combination with nitrite for a period of 80 weeks without any reported incidence of tumour development. However, details on experimental methodology/parameters (such as dose, formulation, numbers within treatment groups, and toxicities) were not provided, and no assessment can be made of these cited findings.

The TGA requested information from the sponsor to address these deficiencies, either in the form of new nonclinical studies or by providing sufficient justification for their absence in the dossier. In response, the sponsor argued against the necessity for extensive genotoxicity testing in view of the widespread use of cyclizine over the years, which has not shown incidences of '*any pregnancy-related problems as would be expected if cyclizine had significant mutagenic properties*'. To support this statement, the sponsor submitted an additional clinical study (Nelson and Forfar, 1971), which was referred to the clinical evaluator for further assessment and comment on the validity of the statement above.

The sponsor also cited previously submitted carcinogenicity data to support their argument of negligible genotoxic risk. However, as described above, the details of this study were grossly inadequate to enable any valid assessments and extrapolations on the potential genotoxic, let alone carcinogenic, risk of cyclizine. The lack of carcinogenicity studies can be acceptable for a medicine used for only short periods[5], although in the case of cyclizine, genotoxicity testing was also very limited.

It bears mentioning also that none of the cited studies used the same formulation and salt (cyclizine lactate) as the product intended for registration. This is of significance because the one submitted genotoxicity study showed nitrosated cyclizine (which forms under acidic conditions) to give rise to mutations in some bacterial strains and the product specifications indicated that cyclizine lactate solution has a pH range of between 3.3–3.7. Therefore it might still be prudent for the sponsor to conduct more thorough investigations on the genotoxic properties of cyclizine to definitively assess whether in its form it could potentially generate species that may be genotoxic. Otherwise, in the absence of adequate nonclinical data or justification, a qualified risk assessment of cyclizine cannot be made to determine the potential genotoxic risk of cyclizine.

Reproductive toxicity

Reproductive toxicity data were obtained from papers published between 1963-1972, with studies conducted in rats, mice and rabbits. This period preceded the development of nonclinical guidelines for reproductive toxicity assessment, and the study designs described in these published reports do not follow the current guideline-endorsed approaches. Thus, no studies examined the potential effects of treatment during the pre-coital period or later than late gestation, including postnatal treatment. All studies examined treatment of animals during gestation, although the timing of exposure during the gestational period was variable both among studies and even within the same study, confounding the interpretation of the results. One study (using rats, mice and rabbits) used both PO and parenteral administration, but the parenteral route was not defined. Another study had no untreated control group. There were also no kinetic studies investigating placental transfer or excretion into milk. On a more general note, none of the animal studies reported mortalities or any evidence of maternal toxicity, suggesting that tested dose levels were only modest and could have been escalated.

Nevertheless, some relevant information could be derived from the composite data. In general, rats exposed to cyclizine during gestation displayed a dose-dependent increase in both resorptions and malformations, with the highest tested dose (125 mg/kg/day PO, on gestation day (GD) 12-15) causing complete fetal resorption. A NOEL for reduced fertility was not

[5] The *need for carcinogenicity studies of pharmaceuticals.* pp. 73-78 (3BS8a) of *The Rules Governing Medicinal Products in the European Union* - EudraLex - Medicinal products for human use, 1998 Edition: Volume 3B - Safety and the Environment

established. In two studies the NOEL for malformations was 50 mg/kg/day for dosing during late organogenesis (GD 12-15); with a more extensive dosing period (GD 1-15), a low level of malformations was noted, although the resorption rate was high. At a higher dose (75 mg/kg/day, GD 12-15), both resorptions and malformations were unequivocal. In another study, a NOEL for malformations was not established (< 25 mg/kg/day, GD 1-16).

In the mouse, malformations were seen at 50 and 75 mg/kg/day, but not consistently, although the high degree of resorptions (100% at 75 mg/kg IP, GD 1-13) may have masked the actual incidences of malformations since they themselves may have induced resorptions. In the rabbit, resorptions occurred only at the 75 mg/kg/day dose but there was a dose-dependent increase in fetal malformations including problems with eye development, spina bifida and microcephaly, with a threshold dose of approximately 25 mg/kg/day.

Clinical reports concerning the incidence of teratogenicity were also provided by the sponsor, which (although published over 40 years ago) indicated relatively low incidences of fetal abnormalities that could be associated with cyclizine use. These reports were referred to the clinical evaluator.

In response to a TGA request for information, the sponsor cited animal studies showing a teratogenic effect by cyclizine, which the sponsor indicated has been proposed to be due to a mechanistic effect involving "*binding of an active metabolite of these compounds to cartilage (to) displace calcium and the induction of foetal oedema as a simple mechanical cause for the observed orofacial malformations*". The source of this information is unclear and the cited reference by King *et al*., 1965 made no specific mention of a mechanistic effect accounting for teratogenicity by cyclizine. The sponsor indicated that the relevance of this mechanism in humans should be easy to validate but did not provide further details on how this was the case. The sponsor's response referred to previously submitted epidemiological investigations, and included a new reference (Nelson and Forfar, 1971) and adverse drug reactions (ADRs) relevant to Reproductive Toxicity. These were referred to the clinical evaluator for assessment as to whether they support the assertions of the sponsor with regard to the use of cyclizine during pregnancy.

Nonclinical summary and conclusions

- The supporting nonclinical data were solely in the form of published reports, with no additional studies carried out by the sponsor. Document quality was variable and generally low, a limitation acknowledged by the sponsors, because most of the nonclinical studies were published many years ago prior to GLP-compliance and regulatory guidelines.
- Cyclizine is a piperizine-derivative histamine H_1 receptor antagonist with reported antimuscarinic actions, known for this class of substances. The nonclinical data used to demonstrate primary pharmacodynamic efficacy were limited to one early study (from 1954) that documented an antiemetic effect by cyclizine in an experimental model of emesis, with little/no data presented that explored the dose-dependency, efficacy, selectivity and/or mode of action. Limited experimental data showed antihistamine but not anticholinergic activity. Evidence of efficacy will need to rely on the clinical data, including its history of clinical use as an antiemetic.
- In the published safety pharmacology studies (the majority published prior to 1990), only the cardiovascular and central nervous systems were (minimally) investigated (for example, no ECG or hERG assays were performed). In rats, PO cyclizine (≥ 75 mg/kg/day) was associated with pancreatic pathology and plasma glucose/insulin changes.
- Pharmacokinetic data were limited, including no exposure measurements from the toxicity studies. In rats, cyclizine was found to be distributed to lung and other tissues. Metabolic pathway analysis (greyhound urine) showed norcyclizine as the major metabolite (demethylation); others included monohydroxylated and basic compounds, and N_1-dealkylation products, many as Phase II conjugates. The primary human metabolite was

also norcyclizine, which had negligible antihistaminic properties. Cyclizine inhibited human hepatic estrone sulfotransferase and murine MAO-B, but showed only weak inhibition of human CYP2D6 and 2C9.

- The one repeat dose toxicity report (dietary administration in rats) noted liver changes (enlarged/spotted at 142 mg/kg/day, light-coloured at 26 and 59 mg/kg/day) and pulmonary oedema (142 mg/kg/day), but few other effects. There were no exposure data.
- Genotoxicity assessment was limited to one Ames test, in which mutations were only seen when cyclizine was in a nitrosated form; this may be relevant for PO administration if nitrites are present in food. There were no carcinogenicity studies; a cited study noted no tumours in rats fed cyclizine with nitrite for an 80 week period.
- Published reproductive toxicity studies examined PO cyclizine administration in rats, mice and rabbits during gestation, with evidence of resorptions and malformations in all species, although NOEL values were not consistent across the (variable) study designs. There was no evidence of maternal toxicity. Placental transfer, excretion into milk and maternal exposure measurements were not conducted.

Conclusions and recommendations

Based on current regulatory guidelines and GLP standards required for nonclinical studies to support the registration of an NCE, the nonclinical dossier submitted for the registration of cyclizine (Valoid) is not adequate. Studies used to support the primary pharmacodynamic effects of cyclizine did not sufficiently demonstrate efficacy for the proposed indication or mechanism of action. Safety pharmacology was also minimally investigated, and there were no follow-up studies of the pancreatic effects reported in rats. Kinetic studies did not determine exposures in the species used for toxicological studies, so comparisons with anticipated clinical exposure were not possible. Metabolism was studied only in dogs (a species that was not used for any of the toxicity tests), and it is unknown whether the potential toxicity of human metabolites was assessed in the animal studies. Repeat dose toxicity was confined to one 12 week dietary study in rats. Although the lack of carcinogenicity studies is acceptable for a medicine used for only short periods, genotoxicity testing was very limited (one bacterial mutation assay using a low cyclizine concentration). Reproductive toxicity studies were also inadequate, with no pre-coital or postnatal exposure investigated.

The nonclinical dataset needs to be assessed in view of CPMP/SWP/799/95[6], which describes the acceptable nonclinical requirements for the registration of medicines with an extensive clinical history. In these cases, many traditional nonclinical studies are not required if all aspects of clinical efficacy and safety have been addressed by clinical experience; however, nonclinical data on genotoxicity and embryofetal and peri/postnatal development may still be required. In view of these issues, the clinical evaluator will need to be assured that the identified nonclinical deficiencies are adequately offset by sufficiently well-documented clinical information.

IV. Clinical findings

Introduction

Cyclizine is a well established antiemetic and has been used parenterally in routine clinical practice for more than 50 years. There is also evidence of clinical need in Australia. Currently, 60,000 Valoid ampoules are provided for the Australian public on a named patient basis each year.

Clinical data comprised a literature based submission (with approximately72 references) to register a NCE. In relation to NCEs and literature based submissions the following statement is made in a TGA guideline: *Under exceptional circumstances, however, literature Based*

[6] *Guideline on the non-clinical documentation for mixed marketing authorisation applications*, 13 October 2005.

Submissions (LBS) may be accepted for medicines, which, although they may have been marketed in other countries for many years, are considered new chemical entities (NCE) in Australia because they have never been marketed here[7].

Many of the references provided were very poor quality copies, some unreadable, others unable to undergo useful text recognition so that rather than cut and paste quotations had to be retyped. This delayed assessment. The nonclinical submission also contained some clinical reports.

Because of conflicting information in the dossier, the sponsor's clarification was sought on the proposed indications. The sponsor subsequently confirmed that the intended indications are:

- the treatment of nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period
- pre-operative use in patients undergoing emergency surgery to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia

The evaluator considered the first indication is ambiguous, being readily interpreted as two indications:

- The treatment of nausea and vomiting caused by narcotic analgesics and
- The treatment of nausea and vomiting caused by general anaesthetics in the post-operative period.

The evaluator assessed the submitted evidence accordingly, noting that post-operative vomiting associated with local anaesthesia was shown by Bonica *et al*., 1958 to be considerably less frequent than with general anaesthesia. Further the evaluator believes that the only pivotal study that was clearly associated with local anaesthesia (Nortcliffe *et al*., 2003; all patients received ephedrine as needed (PRN); patients received cyclizine at the end of surgery, morphine was given intrathecally with fentanyl and heavy bupivacaine prior to surgery[8]) was confounded by the use of ephedrine (as well as intrathecal opiate). The other study that may have been associated with local anaesthesia (Hildyard *et al*., 2001) was an abstract only, submitted with limited data.

Literature search

The search strategy was based on the current indications for Valoid in the United Kingdom (UK). These indications however had been partly based on historical data and, by extrapolation to data on the use of the oral formulation of cyclizine. It was found that the clinical data available in the literature was insufficient to support all claims that had featured in the literature search strategy. Therefore the claims in the proposed PI are limited to:

> *The prevention and treatment of nausea and vomiting:*
>
> *Nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period*
>
> *Valoid may be given pre-operatively in patients undergoing emergency surgery in order to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia.*

In email correspondence, the TGA informed the sponsor that the search strategy was acceptable.

[7] TGA guideline on Literature Based Submissions Points to Consider, available at http://www.tga.gov.au/pdf/pm-literature-based-submissions.pdf.

[8] All patients received ephedrine PRN; patients received cyclizine at the end of surgery, morphine was given intrathecally with fentanyl and heavy bupivacaine prior to surgery.

Good clinical practice

The submission was literature based. None of the cited studies in this report was carried out according to Good Clinical Practice.

Pharmacokinetics

These were submitted for 1 volunteer after 50 mg PO (Walker and Kanfer, 1987) and 6 healthy volunteers after 25 mg IV (Walker and Kanfer 1996). Measurement was by HPLC with a lower limit of quantitation (LLOQ) of 1 ng/mL and a relative standard deviation (SD) and accuracy of ≤ 10% for both cyclizine and norcyclizine in serum and urine. Further data on 1 volunteer after 50 mg PO (Griffin and Baselt, 1984), and 1 after 50 mg IV was found (Land *et al*., 1981).

Figure 1. Cyclizine serum concentration-time profile in a human subject after the administration of a single 50 mg PO dose (from Walker and Kanfer, 1987)

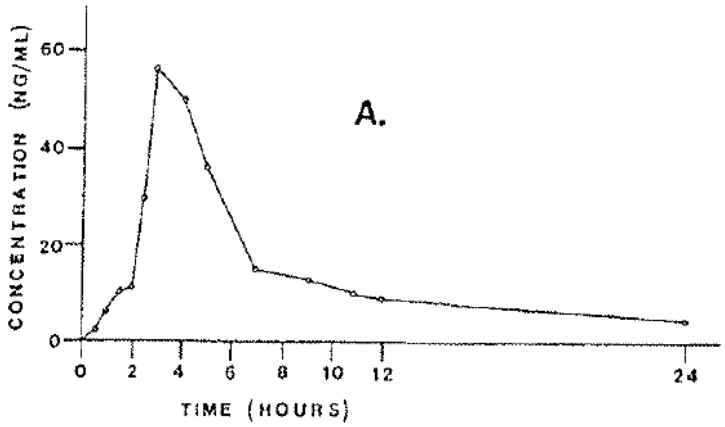


Figure 2. Urinary excretion plot of cyclizine after the administration of a single 50 mg PO dose (from Walker and Kanfer, 1987)

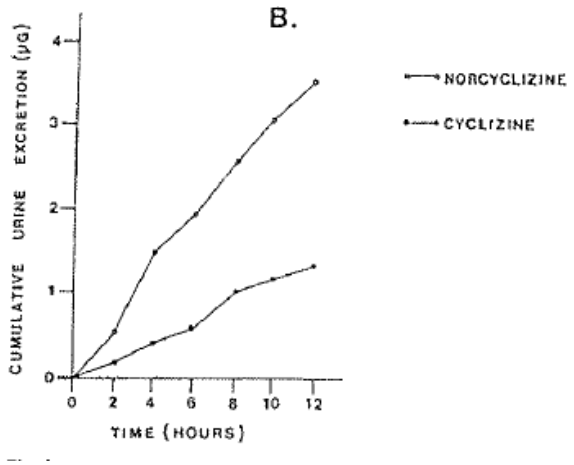
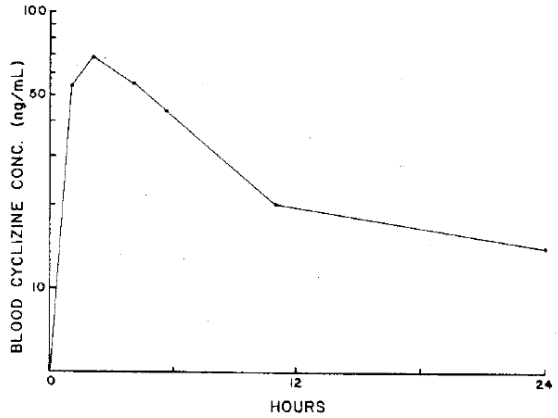
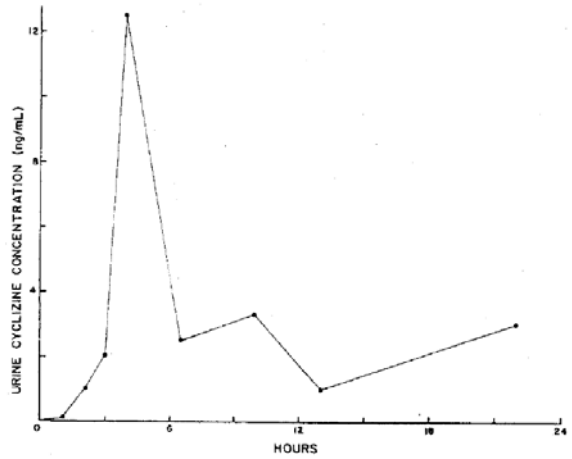


Figure 3. Blood cyclizine concentration profile for an adult subject following PO ingestion of 50 mg of cyclizine hydrochloride (from Griffin and Baselt, 1984)



Blood levels declined in a biphasic manner, with estimated half-lives of 7 h and 24 h for the early and late phases, respectively.

Figure 4. Urine cyclizine concentration profile for an adult subject following PO ingestion of 50 mg of cyclizine hydrochloride (from Griffin and Baselt, 1984).



The 24 h urinary excretion of unchanged cyclizine amounted to only 0.01% of the administered dose.

Table 1. Cyclizine pharmacokinetics for subjects 1 to 6 following administration of an IV bolus dose of 0.5 mL of a cyclizine lactate solution (50 mg/mL) (from Walker and Kanfer, 1996).

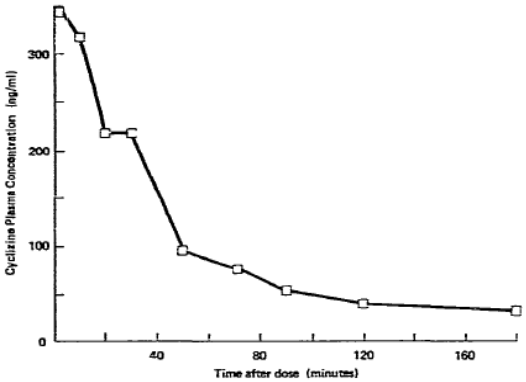
Subject	$AUC_{0-\infty}$ µg/L*h	MRT h	λ_z h^{-1}	$t_{1/2}$ h	V_{ss} L/kg	V_z L/kg	Cl_{TOT} L/h/kg	Cl_R	% dose in urine
1	237.63	15.16	0.0492	16.52	15.68	21.04	1.034	0.00361	0.53
2	259.00	15.62	0.0510	13.58	11.38	14.29	0.729	0.00934	1.03
3	324.89	15.64	0.0562	12.32	12.32	14.01	0.788	0.00186	0.32
4	253.97	12.57	0.0658	10.53	11.06	13.37	0.879	0.00277	0.46
5	263.02	19.74	0.0433	16.00	17.32	20.23	0,877	0.00442	0.41
6	300.65	14.03	0.0568	12.21	12.82	16.10	0.914	0.00306	0.57
Mean	273.53	15.46	0.0537	13.53	13.43	16.50	0.870	0.00418	0.55
SD	32.53	2.40	0.0077	2.33	2.51	3.33	0.105	0.00244	0.25

MRT = mean residence time (MRT), which is the time when 63.2% of an IV has been eliminated from the pharmacokinetic system. λz = the terminal rate constant. Vz = the apparent volume of distribution. V_{ss} = the volume of distribution at steady state. Cl_{TOT} = total clearance. Cl_R = renal clearance. Note this is derived from a poor copy of Table 1 in Walker and Kanfer, 1996).

From Walker and Kanfer, 1996: *"The mean value of 15.50 ± 3.53 L/kg for V_z clearly indicates extensive distribution of cyclizine. A high value for V_z is expected since experiments in which cyclizine was administered to male rats resulted in concentrations of cyclizine in the lung, spleen, liver and kidney 20–110 fold higher than those in plasma (Kuntzman et al, 1965). Norcyclizine, the main metabolite, was isolated in the urine but was conspicuously absent in serum. Metabolic inactivation of cyclizine, primarily by demethylation (Kuntzman et al, 1965) to form norcyclizine or by glucuronidation (Luo et al, 1991) in the liver, is an indication that extrarenal clearance accounts for most of the removal of drug from the body. In addition, renal clearance of cyclizine and norcyclizine were negligible with less than 1% of the dose excreted up to 36 h and the presence of norcyclizine in urine emphasises that alternative mechanisms of elimination are responsible for the removal of cyclizine from the body. Current utilization of oral cyclizine and its associated dosage recommendations (4-6 hourly) are apparently based on a much shorter half-life, implying that chronic use may result in accumulation of the drug based on the terminal elimination half-life of approximately 13 h established in this study."*

Land *et al*., 1981 reported a peak level of approximately 350 ng/mL after IV administration of a 50 mg dose.

Figure 5. Plasma cyclizine profile in healthy adult male subject after administration of 50 mg cyclizine IV (from Land *et al*., 1981).



The delay in excretion seen in the plasma profile at around 30 min is well known for basic drugs (for example, amphetamine).

Luo *et al*., 1991 gave 2 volunteers 2 doses of 30 mg of cyclizine 6 h apart; urine was collected for a period of 36 h from the first dose. 16.9% and 11.7% of the dose was excreted in the volunteer's urine as N^+glucuronide. N^+Glucuronidation also occurs at the piperazine ring of cyclizine, specifically at the N-methyl substituent.

Evaluator's overall conclusions on pharmacokinetics

The major deficiencies are:

- The lack of repeated dose studies or a pharmacokinetic model on which to base dosage recommendations.
- The lack of a bioequivalence study for IM dosing.

In a justification for not providing appropriate biopharmaceutic studies (Module 1.11.2 of the dossier), the sponsor argues that:

- The known physical properties of cyclizine demonstrate that it would be highly permeable across tissue.
- Administration of the doses by the IM route would be unlikely to affect the plasma half life since the same tissue diffusion mechanisms pertain after distribution into tissue from the IV injection.
- An IM injection would likely result in lower initial plasma levels with possible incomplete suppression of symptoms prior to peak levels being reached.

Unfortunately in this section the sponsor also quotes a plasma half life of approximately 20 h whereas Walker and Kunfer, 1966 gives a mean of 13.53 h.

The sponsor also states in the justification section that: *"Cyclizine has been approved across worldwide markets at single doses of 50 mg given orally, by IV or IM injection."*

Pharmacodynamics

Primary pharmacodynamic effects

Vestibular function

Reicke (1976) tested the nystagmus produced by a rotation and head tilt test (Coriolis effect) to assess peripheral vestibular function and its modification by 50 mg PO cyclizine.

While nausea was reduced, there was no effect on nystagmus. Reicke interpreted this as indicating a central action on the vomiting centre rather than the peripheral vestibular function. However Reike quoted Gunter *et al*., 1954 as seeing a marked reduction on vestibular function testing with 100 mg cyclizine, but 50 mg had variable effects.

Gowans *et al.,* 2000 looked at the effects of 50 mg of PO cyclizine on visual-vestibular interactions in humans, and found no significant suppressive effect on postural sway and circularvection; optokinetic nystagmus initial slow phase velocity was significantly increased ($p < 0.05$), although optokinetic nystagmus amplitude and frequency were unaffected. Again suggesting that cyclizine 50 mg has minimal suppressive effects on these aspects of visual-vestibular interaction.

In a paper by Gunter *et al*., 1954 ten patients given orally either 50 or 100 mg cyclizine or 100 mg chlorcyclizine were investigated with the cold microcaloric test and galvanic stimulation of the mastoid area. Figures 6-8 and Table 2 are from Gunter *et al.,* 1954:

Figure 6. Onset of nystagmus.

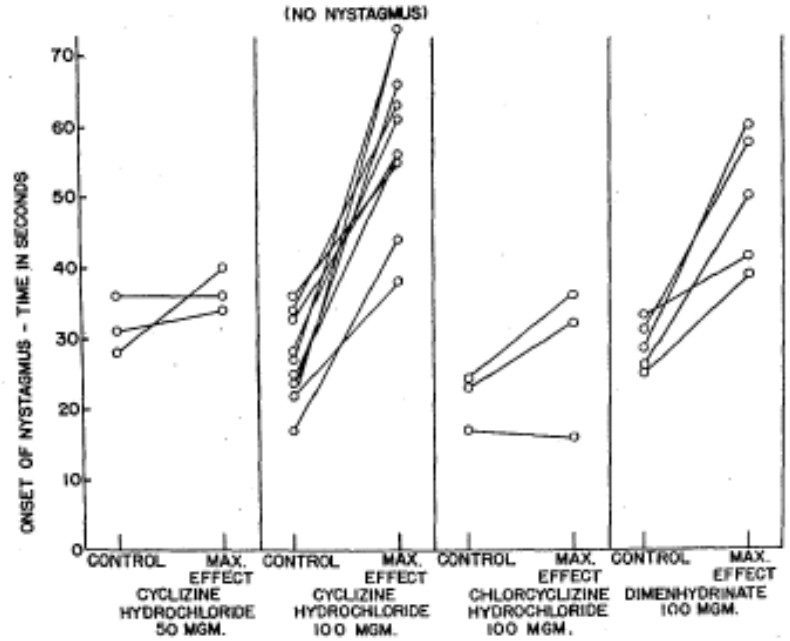


Figure 7. Duration of nystagmus.

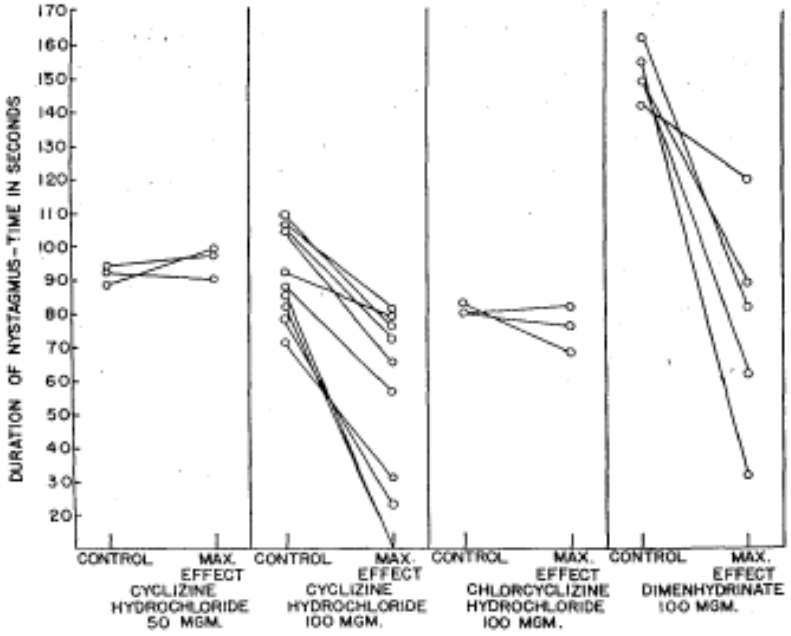


Figure 8. Ratio of time of onset to duration of nystagmus

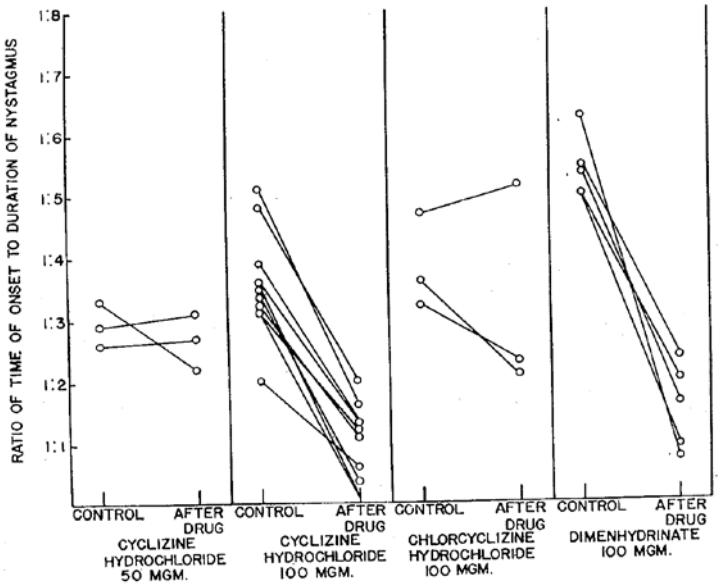


Table 2. Influence of cyclizine HCL on vestibular function measured by Galvanic Stimulation Method

Subject	Age, Yr.	Dosage, Mg.	Milliamperes Required for Tilting: Control	Cyclizine 1	Cyclizine 2	Cyclizine 3	Per Cent of Change
S. D.	62	50	3	3	3.5	3.5	17+
		100	4	5.5	No tilt *		No tilt
B. K.	25	50	3	3	3	3	0
		100	3	4	5	5	67+
A. G.	46	50	3	3	3	3	0
		100	2.5	5	5	5	100+
M. S.	24	100	3	5	No tilt		No tilt
M. B.	15	100	3		No tilt		No tilt
E. K.	41	100	3		No tilt		No tilt
B. S.	64	100	3	4.5	5	5	67+
A. F.	50	100	3	4	No tilt		No tilt
R. R.	32	100	3	4.5	5	5	67+
J. N.	29	100	3	4	5	5	67+

*"No tilt" indicates tilting could not be made to occur before the rising milliamperage exceeded the patient's local tolerance.

Secondary pharmacodynamic effects

Drowsiness

Lederer and Putnam (1958) looked at subjectively reported drowsiness in 100 subjects after 50 mg PO cyclizine: 14 had Mild-effects that were not enough to interfere with normal class routine; 10 had Moderate-effects that were severe enough to interfere with class routine; 4 had Severe-effects that interfered with class routine and social activity to the point of moderate or severe incapacitation, requiring bed rest. Placebo produced 2 mild, 5, moderate and 1 severe drowsiness reactions.

Brand *et al*., 1968 looked at subjectively reported drowsiness in a motion sickness inducing situation with 58 subjects. Drowsiness was dose related: placebo 54%, cyclizine: 15 mg 55%, 25 mg 66%, 40 mg 78%, 65 mg 71%, 100 mg 79%. They also looked at the effect on mental performance and noted an improvement against placebo in mental arithmetic: cyclizine: 15 mg 10.8%, 25 mg 11.5%, 40 mg 7.2%, 65 mg 14.0%, 100 mg 18.3%. The explanation given was that the effect on mental performance of nausea was greater than the effect of medication in those who had no nausea (there were however a significant number vomiting in all groups: placebo 55%, cyclizine: 15 mg 35%, 25 mg 35%, 40 mg 28%, 65 mg 24%, 100 mg 21%).

Subsequent arithmetic testing (Brand *et al*., 1968) in the absence of motion could show no drug effect with 15 or 100 mg.

Clubley *et al*., 1979 looked at performance and vigilance with a battery of tests under laboratory conditions with 2 groups of 12 subjects taking placebo (lactose), or cyclizine 25 and 50 mg a week apart, or placebo, or cyclizine 50 and 100 mg a week apart. Values after cyclizine 25 and 50 mg did not differ from those after lactose for the number of signals detected over 1 h in the auditory vigilance test, auditory reaction time tested over 15 min and tapping rates. There were no changes ascribable to treatments in arithmetic, digit symbol substitution test or digit symbol substitution test.

In Trial group 2 cyclizine 50 or 100 mg produced no changes in auditory vigilance significantly different from those following lactose, but the number of detections was lower after cyclizine 100 mg. Mean values in reaction time were longer after cyclizine 50 and 100 mg than lactose; 5-5.25 h after cyclizine 100 mg the number of sums completed was reduced compared with lactose. This was the only performance test in which cyclizine differed significantly from lactose. The only significant subjective effect after cyclizine was increased mental sedation at 6 h after the 100 mg dose. The energy in the delta frequency band was greater 2.8 h after cyclizine 100 mg than after both lactose and cyclizine 50 mg; by 6.1 h the energy in the delta band was still significantly higher after cyclizine 100 mg compared with cyclizine 50 mg but not lactose. There were no differences in the alpha, beta and theta bands at 2.8 h or 6.1 h after treatment between cyclizine 50 or 100 mg and lactose.

Haemodynamics

Clubley *et al*., 1979 also monitored heart rate by recording classical limb lead I. There were no treatment effects on heart rate in either trial group.

Bassett *et al*., 1996 in reviewing 80 teenage cases of abuse reporting to the Utah Poisons Centre (of whom only 25% had co ingestions) found that 52% had tachycardia (> 115 beats/min), 69% had systolic hypertension (> 135 mmHg), 15% had diastolic hypertension, and 14% had fever (> 38°C).

Effect on lower oesophageal sphincter

Brocke-Utne *et al*., 1977 and 1978, in 2 different journals' reports of 2 studies reported on 8 awake and healthy volunteers in each study receiving 25 mg cyclizine IV. They showed in both studies that the basal barrier (due to sphincter) pressure increased from a basal mean pressure of 19.1 cm H_2O to 33.5 cm H_2O ($p < 0.005$). The results in the second (1978) study, for all parameters measured, are identical except they are reported in kilopascals (kPa). There was no reference to them being the same subjects, indeed the 1978 study contains the statement: *"Both cyclizine and metoclopramide increased barrier pressure significantly, thus confirming previous reports indicating that these two drugs increase LOS tone (…Brock-Utne et al., 1976[9]; Brock-Utne et al., 1977)"*.

[9] There was no Brock-Utne *et al.,* 1976 among the list of references and a handwritten note on the submitted article suggests it doesn't exist.

Table 3. Gastro-oesophageal pressures before and after cyclizine.

	Basal	After cyclizine
Gastric pressure		
Mean	26,4	26,2
SEM	1,54	1,53
Sphincter pressure		
Mean	45,5	59,7
SEM	2,55	3,07
Oesophageal pressure		
Mean	5,4	5,7
SEM	1,11	1,21
Barrier pressure		
Mean	19,1	33,5
SEM	2,36	2,56

Source: Figure 1 from Brock-Utne *et al*., 1977.

Genetic-, gender- and age-related differences in pharmacodynamic response

A study by Tan *et al*., 1988 in patients with severe heart failure showed deterioration in cardiovascular function and is considered in the *Safety* section below.

Pharmacodynamic interactions

Nil discussed in submission. However Clubley *et al*., 1979 included a comparison with groups on caffeine and cyclizine combinations, not relevant to the submission.

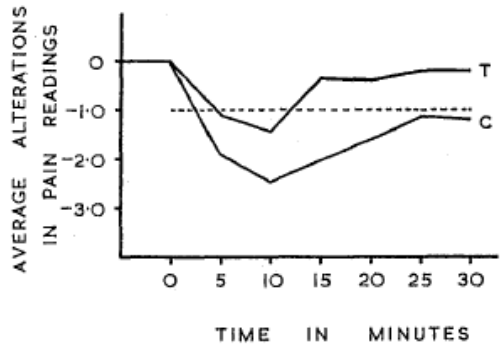
Back *et al*., 2007 state: *"There is evidence that cyclizine inhibits CYP2D6,*[10] *and also that CYP2D6-inhibiting H_1-antihistamines can increase the plasma concentrations of haloperidol*[11] *(a CYP2D6 substrate)."*

The addition of cyclizine to haloperidol (as in the patient described, and as is common practice) may therefore in itself result in a higher plasma level of haloperidol, and thus an increased risk of adverse effects.

Antanalgesic effects

Nicholl *et al*., 1962 compared the analgesic index[12] (alterations in pain threshold and response readings) before and after injections including cyclizine 50 mg IV to 6 healthy patients. Cyclizine had considerable antanalgesic effect compared to other drugs then used as shown in the following.

Figure 9. Average effects of the IV injection of cyclizine 50 mg (C) and trimethobenzamide 200 mg (T) on the mean of the threshold and response readings.



Each drug was studied in six subjects.

[10] He *et al*., 2002.
[11] Suzuki *et al*., 2003.
[12] Reference describing this was not submitted.

Table 4. Analgesia indices of drugs studied

Premedication	Analgesia index
Atropine 0.6 mg	+0.04
Trimethobenzamide 200 mg; atropine 0.6 mg	+0.02
Cyclizine 50 mg; atropine 0.6 mg	−0.49
Pethidine 100 mg; atropine 0.6 mg	+0.55
Trimethobenzamide 200 mg; pethidine 100 mg; atropine 0.6 mg	+0.57

Comment: Some (but not all) of the efficacy studies submitted appear to support this, for example, O'Brien *et al.,* 2003.

Table 5. Morphine administration by antiemetic (from O'Brien *et al.*, 2003)

	Ondansetron	Normal saline	Cyclizine
Morphine given	9	9	12
Vomited	1 (11%)	3 (33%)	5 (41%)

Relationship between drug concentration and pharmacodynamic effects

Brand *et al.* (1967) showed a linear log dose-response curve for PO cyclizine:

Figure 10. Log. Dose-response curve. (-)-Hyoscine (●) and cyclizine HC1 (X) (placebo vomiting rate, 55%).

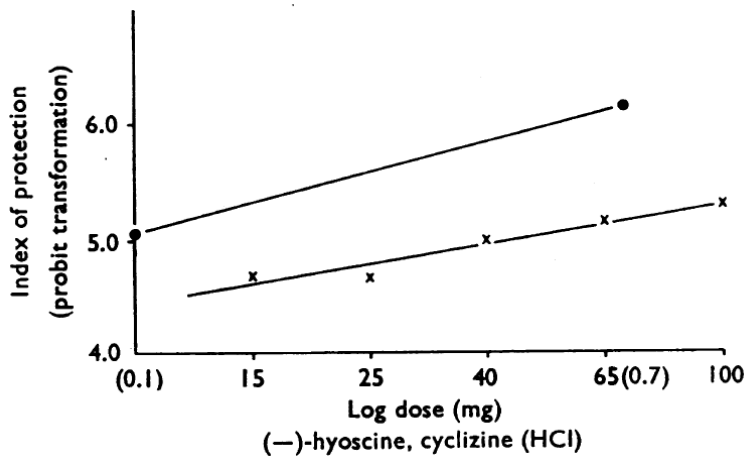


Table 6. Response index of protection (from nausea & vomiting).

	Dose (mg)	Response index of protection, as probit
Cyclizine	15	4.68
Cyclizine	25	4.68
Cyclizine	40	5.0
Cyclizine	65	5.16
Cyclizine	100	5.30

Evaluator's overall conclusions on pharmacodynamics

There appears to be a reputation for the drug having *"few significant side effects"* (as O'Brien *et al*., 2003 put it). However many of the adverse events (AEs) reported relate to the actions of the drug. The relatively few pharmacodynamic and efficacy studies suggest effects on vestibular function, drowsiness, haemodynamics, lower oesophageal sphincter and antanalgesic effects. The problem lies in determining to what extent the effects relate to dose, route of administration and individual sensitivity. What evidence there is showed vestibular effects only for 100 mg orally; drowsiness was shown in some patients in some studies; haemodynamic effects were seen in overdose and revealed at the proposed dose IV to the detriment of patients in cardiac failure.

Efficacy

Dosage selection for the pivotal studies

There was no discussion of the effective dosage in the [sponsor's] *Clinical Summary* or the *Cochrane review* (Carlisle J and Stevenson CA, 2006). As already stated, deficiencies [in the clinical data] are:

- The lack of repeated dose studies or a pharmacokinetic model on which to base dosage recommendations.
- The lack of a bioequivalence study for IM dosing.

As mentioned above, the sponsor, in justifying the absence of a bioequivalence study, quotes a plasma half life of approximately20 h whereas Walker and Kunfer, 1966 gives a mean of 13.53 h; and the sponsor argues that: *"Cyclizine has been approved across worldwide markets at single doses of 50 mg given orally, by IV or IM injection."*

Most trials used 50 mg PO or parenteral. However cyclizine in 100 mg dosage notably decreased labyrinthine sensitivity. The results with cyclizine 50 mg were inconsistent and variable (Gutner *et al*., 1954).

With regard to frequency of dose again this was not discussed, but: *"Current utilization of oral cyclizine and its associated dosage recommendations (4-6 hourly) are apparently based on a much shorter half-life, implying that chronic use may result in accumulation of the drug based on the terminal elimination half-life of approximately 13 h established in this study"* (Walker and Kanfer, 1996).

Comment: The evaluator's experience of the drug used post middle ear surgery (for example, stapedectomy) was 100 mg IM 8 hourly, but for not more than 24 h. When used beyond this duration on a continuing 8 hourly basis, CNS (extrapyramidal) effects tended to occur. It is clear from the studies that 50 mg PO, IM or IV are considered appropriate doses: Brand *et al.* (1967) used 15-100 mg PO, Lederer and Putnam (1958) used 50 mg PO, Gunter *et al*. (1954), looking at the effect on nystagmus (inner ear) found 50 mg ineffective compared with 100 mg PO, Nicholl *et al*. (1962) used 50 mg IV.

All the efficacy studies on post operative and opiate induced nausea and vomiting used 50 mg IM or IV. Brocke-Utne *et al.* (1977, 1978) however showed 25 mg IV was effective on the lower oesophageal sphincter pressure.

Nausea and vomiting caused by general anaesthetics in the post-operative period

The evaluator agrees with the sponsor that anaesthetic techniques have changed considerably over time. Regional anaesthesia was often accompanied by some supplementation. While this may have been general anaesthesia (GA) (usually for intra-abdominal procedures), the alternative was heavy sedation that usually included a phenothiazine and an opiate.

Bonica *et al.* (1958) showed the considerable variation in incidence of nausea and vomiting with different anaesthetic techniques as well as different surgical sites. This needs to be considered when reviewing study results.

Table 7. Incidence of nausea and vomiting [with] general versus local anaesthesia (Table 3 in Bonica *et al*., 1958)

	Total Number of Cases	Incidence of Nausea, Retching and Vomiting	
		Number	Per Cent
General anesthesia:	1,561	476	30.5
Thiopental alone	36	3	8.3
Thiopental-nitrous oxide	878	127	14.5
Thiopental-nitrous oxide-demerol drip	242	106	43.6
Cyclopropane	232	129	55.6
Ether	173	111	64.2
Regional anesthesia:	1,180	256	21.7
Subarachnoid block	459	101	21.1
Spinal Epidural block	338	75	22.1
Caudal block	203	58	28.5
Paravertebral block	36	10	28.0
Extremity block (block of brachial plexus, sciatic-femoral)	113	10	8.8
Local infiltration of field block	31	2	6.5
Regional anesthesia supplemented with general	86	51	59.3
Total	2,827	783	27.7

Table 8. Relationship of operation site to nausea and vomiting. (Table 4 in Bonica *et al*., 1958)

Site of Operation	Number of Cases	Incidence of Emetic Symptoms	
		Number	Per Cent
Head and neck	418	105	25.1
Chest	159	62	38.4
Abdomen	959	424	44.2
a. Intra-abdominal			
Stomach and duodenum	66	48	72.7
Gall bladder	110	79	71.8
Intestines and appendix	174	85	48.8
Gynecologic	266	110	41.4
Cesarean section	119	44	37.0
Renal	18	7	38.8
Abdominal wall	206	31	15.0
Back	119	34	28.5
Perineum and extremities	1,172	178	15.1
Total	2,827	783	27.7

Le and Gan (2010) refer to the [Apfel] scoring system of four highly predictive risk factors for post-operative nausea and vomiting (PONV): female gender, history of motion sickness or PONV, non smoker, and use of perioperative opioids. The presence of 0, 1, 2, 3, or 4 of these factors corresponded to a PONV incidence of 10%, 21%, 39%, 61%, and 79%, respectively. However, while higher Apfel scores correlate to a greater incidence of PONV symptoms in the early (0-24 h) postoperative period, it appears to have little predictive value for emetic symptoms occurring in the late (24-72 h) postoperative/post discharge period. Sinclair *et al.* 1999 (taking in 3 year and 17,000 patients) added to these 4 factors; duration of anaesthesia longer than 30 min, general anaesthesia, and type of surgery, as independent predictors of PONV. The following table is from Le and Gan (2010).

Table 9. Risks factors for PONV and post-discharge nausea and vomiting (PDNV)

Patient Factors	Anesthetic Factors	Surgical Factors
Female	Use of perioperative opioids	Duration of surgery
Nonsmoker	Use of volatile anesthetics	Type of surgery, including:
History of motion sickness or previous PONV	Nitrous oxide	Abdominal
		Ear, nose, and throat
Family history of motion sickness or PONV (pediatric)		Gynecologic
		Laparoscopic
Age ≥3 y (pediatric)		Ophthalmologic
		Orthopedic
		Plastic
		Strabismus (pediatric)

All of the studies in the following tables were prospective, randomised, blinded with 50 mg cyclizine given parenterally (Walder and Aitkenhead, 1995 also included an infusion).

Table 10. Efficacy: the treatment of nausea and vomiting caused by general anaesthetics in the post-operative period - Principal Studies

Study [by date]	Study objective	Premedication	Patients receiving Cyclizine			
			Route	Time	No.	M/F Mean age years (range)
Grimsehl *et al*, 2002[d]	Difference in the incidence of PONV cyclizine verses (vs.) ondansetron	NK[1]	IV	Induction	37	F 31 (SD 6)
Cholwill *et al*, 1999[c]	Incidence of PONV and use of escape antiemetic vs. placebo and ondansetron	NK[1]	IV	Immediately prior to induction	57	F 31 (22-42)
Watts, 1996[c]	Incidence of PONV (historical) and vs. after ondansetron and metoclopramide	temazepam	IV	Prior to induction	53	F 30.3
Chestnutt and Dundee, 1986[c]	Comparison of the safety and efficacy vs. perphenazine and placebo	opiate (meptazinol) alone or plus study drug	IM	About 1.5h prior to surgery[2.] Surgery took 8–15 min	40	F 33 (SD 11)
Dundee *et al*, 1975[c]	Incidence of PONV vs. perphenazine and placebo	morphine or pethidine alone or plus study drug	IM	About 1.5h prior to surgery. Surgery took 5-10 mins	300	F NK

NK = not indicated in report [1] Day surgery cases probably no premed. [2] Based on figure 1 in the study [c] Double-blind SD = standard deviation

Table 11. Efficacy: the treatment of nausea and vomiting caused by general anaesthetics in the post-operative period - Supporting Studies

Study	Study objective	Premedication	Patients receiving Cyclizine			
			Route	Time	No.	M/F Mean age years (range)
Ahmed *et al*., 2000[c]	Difference in the incidence of PONV with placebo, ondansetron alone and in combination with cyclizine	NK[1]	IV	After induction	60	F 32 SD (6)
Johns *et al*., 2006[ab]	Risk of PONV alone or in combination with granisetron	NK[1]	IV	Induction	316	F 41.9 (SD 13.1)
Laffey and Boylan, 2002[c]	The prevention of PONV	diazepam	IV	20 min prior to end of surgery plus infusion in patient-controlled analgesia (PCA)	?14	F ?46
Walder and Aitkenhead, 1995[d]	Reduction of opiate related PONV vs. droperidol	temazepam	IV	20 min prior to end of surgery plus infusion in PCA	25	F 41.9 (SD 11.8)
Dundee *et al*,1966	Comparison of the safety and efficacy vs. trimethobenzamide and placebo	morphine or atropine alone or plus study drug	IM	About 1.5h prior to surgery. Surgery took 6-9 mins	150	F 32

[a] Not included in the Cochrane 2006 meta-analysis [b] The administering anaesthetist was not blind but patients and all other staff remained blind [c] Double-blind [d] Observer blind.

Table 12. Efficacy: Effect on opiate-induced nausea and vomiting

Study	Study objective	Premedication	Patients receiving Cyclizine			
			Route	Time	No.	M/F Mean age years (range)
Dundee and Jones, 1968 [a]	Suppression of oral opiate induced nausea and vomiting	not applicable	PO		83	M 38 F 45 (31-89)
Chestnutt and Dundee, 1986[a]	Reduction in PONV vs. perphenazine and placebo	opiate (meptazinol) alone or plus study drug	IM	About 1.5h prior to surgery[2.] Surgery took 8–15 mins	40	F 33 (SD 11)
Dundee *et al*., 1975[a]	Comparison of the effects vs. perphenazine on opiate related nausea and vomiting	morphine or pethidine alone or plus study drug	IM	About 1.5h prior to surgery. Surgery took 5-10 mins	300	F NK
Dundee *et al*., 1966	Balance of desirable/undesirable effects	atropine or pethidine 100 mg alone or with study drug	IM	About 1.5h prior to surgery. Surgery took 5-7mins	150	F 31.8

NOTE: Chestnutt and Dundee, 1986 and Dundee *et al*., 1975 are listed here as well since they looked at the effect on opiate premed for 90 mins preoperatively.

[a] Double-blind. [b] The administering anaesthetist was not blind but patients and all other staff remained blind. [2] Based on figure 1 in the study.

Efficacy studies considered pivotal by the sponsor

The sponsor, on page 14 of the *Clinical Summary* states:

> *"…twelve clinical studies investigating cyclizine in the prevention of nausea and vomiting caused by narcotic analgesics and by general anaesthetics relating to the period of modern anaesthesia. The studies are Johns et al 2006; O'Brien et al 2003; Grimsehl et al 2002; Nortcliffe et al 2003; Ahmed et al 2000; Cholwill et al 1999; Watts 1996; Walder & Aitkenhead 1995; Chestnutt & Dundee 1986; Dundee et al 1975; Laffey & Boylan 2002 & Hildyard et al 2001."*

Of these the evaluator considers the following are **not** acceptable for evidence for efficacy:

- Hildyard *et al*., 2001: Abstract only was submitted, with limited data.
- O'Brien *et al*., 2003: Antihistamine was used as premedication (PO trimeprazine); outside the age group for [the proposed] indications.
- Nortcliffe *et al*., 2003: All patients received ephedrine[13] PRN; patients received cyclizine at the end of surgery, morphine was given intrathecally with fentanyl and heavy bupivacaine prior to surgery.

Of the remaining studies the evaluator considers that four studies could not be considered pivotal to the proposed indication.

Two studies use dosage and administration differing from that proposed - being given both as an IV bolus of the proposed dose 20 min prior to end of surgery and also an infusion in the PCA:

- Laffey and Boylan, 2002.
- Walder and Aitkenhead, 1995.

One study only made comparison of a combination (that included cyclizine) with another active drug (ondansetron):

- Ahmed *et al*., 2000.

One study had no placebo and only made comparison with a combination (that is, there was no placebo control and there was no statistical comparison given with the other active drug (granisetron), except that the incidence of PONV after discharge from the day surgery unit was significantly higher (confidence intervals not given) in those who had received granisetron:

- Johns *et al*., 2006.

The remaining 5 studies give a total of 487 patients in minor gynaecological surgery.[14] Of these 147 (in 3 studies) would be considered as having had modern techniques for day surgery[15], while 340 (in 2 studies, dated to 1986 and 1975) had an opiate premedication.

The sponsor did not consider one study other than as historical (Dundee *et al*.,1966), yet it really did not differ from Chestnutt and Dundee 1986 or Dundee *et al.,* 1975, except that it was not blinded for the combination of cyclizine and pethidine (one of the groups of interest).

[13] There is evidence of the use of ephedrine as an antiemetic.
[14] The choice of such cases for PONV studies is not unusual – they have a higher incidence and, being short and more of them, numbers are more readily recruited.
[15] Based on the date of publication and the patient selection for day surgery, in the absence of a statement about premedication, the evaluator, based on clinical experience believes none was given in most of these later studies.

Efficacy studies considered pivotal by the evaluator

Cholwill JM, Wright W, Hobbs GJ, Curran J. Comparison of ondansetron and cyclizine for prevention of nausea and vomiting after day-case gynaecological laparoscopy. Br J Anaesth. 1999; 83(4): 611-614.

A double-blind, randomised, placebo-controlled study comparing IV ondansetron 4 mg versus cyclizine 50 mg, for the prevention of postoperative nausea and vomiting for 24 h after day-case gynaecological laparoscopy. Single centre in the UK.

Anaesthesia Induction: propofol 2 mg/kg after alfentanil 10 µg/kg and glycopyrrolate 200 µg. Maintenance: vecuronium 0.05 mg/kg laryngeal mask with intermittent positive-pressure ventilation 33% oxygen in nitrous oxide with added isoflurane to an end-tidal carbon dioxide partial pressure of 4.5-5.0 kPa. Reversal: neostigmine 2.5 mg and glycopyrrolate 200 µg.
Analgesia : 1 h preoperative diclofenac 100 mg PRN; intraoperative morphine 0.18 mg/kg IV Postoperative increments of morphine IV or a combination paracetamol 1 g + codeine phosphate 60 mg orally, PRN.
Inclusion criteria: ASA I or II[16] women undergoing day-case gynaecological laparoscopy, with stratification for past history of PONV.
Exclusion criteria: receiving antiemetic drugs, pregnant, breast-feeding or with body mass index (BMI) > 30 kg/m^2.
Antiemetics: According to randomisation immediately before induction, IV ondansetron 4 mg, cyclizine 50 mg or 0.9% saline (60 per group). Rescue was prochlorperazine 12.5 mg IM.

The study objective was to assess the incidence of PONV and the use of escape antiemetic vs. placebo and ondansetron. The primary outcome measures were the incidence of moderate or severe nausea, vomiting and number of patients receiving escape antiemetic.

The single worst scores for pain, sedation and nausea from any of the three times before discharge and in the period covered by telephone questionnaire (after discharge) were used for analysis. To demonstrate a 50% reduction in the incidence of vomiting or number of patients receiving escape medication (from 30% to 15%) at $\alpha = 0.05$, 180 patients conferred a power of at least 0.8 to the study. Data from patients who received escape treatment were excluded from the post-discharge analysis. Overall comparisons were performed using analysis of variance (ANOVA) or Chi-square (χ^2) tests where appropriate. If a difference was statistically significant at the 5% level, pairwise comparisons were performed. The drugs were blinded to patients, investigators and recovery room staff. Data from this study are shown below.

[16] American Society of Anaesthesiologists (ASA) physical status classification system: ASA I patients are considered to be normal and healthy. ASA II patients have mild to moderate systemic disease or are healthy ASA I patients who demonstrate a more extreme anxiety and fear toward dentistry.

Table 13. Patient demographics

	Ondansetron ($n=60$)	Cyclizine ($n=57$)	Saline ($n=58$)
Age (yr)	31 (22–42)	32 (21–50)	33 (22–46)
Weight (kg)	63 (8)	62 (8)	62 (9)
Height (cm)	164 (7)	164 (6)	165 (6)
Body mass index (kg m^{-2})	23 (2)	23 (3)	23 (3)
Cycle day	17 (9)	17 (9)	16 (8)
Time fasted (h)	9 (3)	9 (4)	9 (4)
Previous PONV (n)	13 (22)	14 (25)	11 (19)
Previous motion sickness (n)	12 (20)	15 (26)	14 (24)
Operation type (n)			
Diagnostic laparoscopy	27 (45)	23 (40)	24 (41)
Laparoscopic sterilization	33 (55)	34 (60)	34 (59)

Data are mean (SD or range) or number (%)

Post operatively before discharge, compared with saline, both ondansetron and cyclizine reduced significantly the incidence of moderate or severe nausea ($p = 0.02$ and $p = 0.001$, respectively) and the requirement for escape antiemetic ($p = 0.04$ and $p < 0.001$, respectively). The incidence of vomiting after ondansetron and cyclizine was less than that after saline (32% and 23%, respectively, versus 41%; $p = 0.1$ overall).

Table 14. Outcomes before discharge in the three groups

	Ondansetron ($n=60$)	Cyclizine ($n=57$)	Saline ($n=58$)
Nausea			
None	27 (45)	27 (47)	17 (29)
Moderate or severe	18 (30)*	3 (23)***	30 (52)
Vomiting	19 (32)	13 (23)	24 (41)
Escape antiemetic	17 (28)*	9 (16)***	27 (47)
Moderate or severe pain	21 (51)	16 (47)	21 (50)
Moderate or severe sedation	17 (28)	17 (32)	10 (18)
Postoperative analgesia			
I.v.	4 (7)	3 (5)	7 (12)
Oral	20 (33)	19 (33)	21 (36)

Data are n (%). *$p < 5$, ***$p < 0.001$ compared with saline

After surgery, 13 patients were admitted 7 with PONV (2 ondansetron and 5 saline patients). These 13 and the 53 patients who received rescue antiemetics were excluded from further analysis. 106/109 remaining patients completed the telephone questionnaire. The incidence of moderate or severe nausea was comparable in all groups. The incidence of vomiting after discharge was reduced with ondansetron and cyclizine compared with saline (not statistically significant).

Table 15. Outcomes after discharge in the three groups and summary data of those suffering no PONV throughout the study.

	Ondansetron ($n=36$)	Cyclizine ($n=42$)	Saline ($n=28$)
Nausea			
None	18 (50)	23 (55)	14 (50)
Moderate or severe	9 (25)	11 (26)	8 (29)
Vomiting	10 (28)	9 (21)	11 (39)
Moderate or severe pain	18 (51)	17 (50)	10 (42)
Analgesia			
Diclofenac	29 (81)	32 (76)	18 (64)
Paracetamol	19 (53)	10 (24)*	14 (50)
No PONV before or after discharge	15 (31)*	17 (33)**	6 (12)

Data are (%). *p < 0.05, **P < 0.01 compared with saline.

The number of patients who had no nausea or vomiting throughout the study was significantly less after either ondansetron and cyclizine compared with saline (p = 0.02 and p < 0.01, respectively).

The authors in the *Discussion* state:

> *"We were surprised that apart from the significant reduction overall PONV throughout the entire study with both ondansetron and cyclizine, there were no other significant differences between groups after discharge. We had expected that cyclizine might have demonstrated greater efficacy after discharge, as it is effective in motion-induced PONV. However, exclusion of patients who had received escape antiemetic in hospital from the post-discharge analysis may explain this observation and support the common conclusion that effective prophylaxis and early control of PONV is an appropriate clinical strategy. Furthermore, this reduction in patient number would have reduced the power of the post- discharge analysis, increasing the likelihood of a type 2 error. Similarly, failure of the reduction in the incidence of vomiting after ondansetron and cyclizine to reach overall statistical significance (P = 0. 1) may also be explained by a type 2 error."*

Grimsehl K, Whiteside JB, Mackenzie N Comparison of cyclizine and ondansetron for the prevention of postoperative nausea and vomiting in laparoscopic day-case gynaecological surgery. Anaesthesia. 2002; 57(1): 61-65.

A randomised, double-blind, active controlled study to compare the efficacy and cost-effectiveness of cyclizine and ondansetron for prophylaxis of PONV in patients undergoing day-case gynaecological laparoscopy. Single centre; UK.

Anaesthesia: Induction: propofol 2-3 mg/kg; fentanyl 1 µg/kg. Maintenance: laryngeal mask 33% oxygen in nitrous oxide with added isoflurane; spontaneous ventilation.
Analgesia: diclofenac PRN prior to start of surgery; postoperative 1-2 mg increments of morphine IV or a combination of paracetamol 1 g + codeine phosphate 16 mg orally, PRN.
Inclusion criteria: ASA I or II women scheduled to undergo either diagnostic laparoscopy or laparoscopic sterilisation.
Exclusion criteria: none listed.
Antiemetics: According to randomisation at induction, IV ondansetron 4 mg or cyclizine 50 mg (37 per group). Rescue was prochlorperazine 12.5 mg IM.

This study was to compare the efficacy and cost-effectiveness of cyclizine and ondansetron for prophylaxis of PONV in patients undergoing day-case gynaecological laparoscopy. The primary outcome measure was the difference in the incidence of nausea between the two antiemetics. The sample size was chosen to show a difference in the incidence of nausea of 35% between the two anti-emetics, based on an α risk of 0.05 and a β risk of 0 .1. The worst scores for nausea prior to discharge and after discharge were used for comparative analysis. Data from patients requiring escape anti-emetic were omitted from subsequent analysis. Comparisons were made using

Student's t-test, Mann-Whitney U-test and Fisher's exact test where appropriate. A Bonferroni correction was made for multiple two-way analyses. Data from this study are shown below.

Table 16. Patient demographics

	Cyclizine ($n = 37$)	Ondansetron ($n = 37$)
Age; years	31 (6)	33 (5)
Weight; kg	66 (11)	63 (11)
Height; cm	163 (6)	160 (6)
Stage of menstrual cycle		
0–8 days	11 [30]	16 [43]
9–16 days	11 [30]	5 [14]
> 16 days	15 [40]	16 [43]
Previous PONV	10 [27]	6 [16]
Type of operation		
Diagnostic laparoscopy	27 [73]	24 [65]
Laparoscopic sterilisation	10 [27]	13 [35]

Data are mean (SD or range) or number (%)

The total incidence of PONV in the first 24 h following surgery was comparable in both groups [cyclizine, 21 (56%); ondansetron, 20 (54%): p = not significant (ns)]

Table 17. Anaesthetic/recovery times and incidence of PONV.

	Cyclizine ($n = 37$)	Ondansetron ($n = 37$)
Anaesthetic time; min	26 (11)	25 (9)
Time to eye opening; min*	10 (4)	8 (2)
Time to discharge; min	309 (49)	324 (68)
Total incidence PONV	21 [56]	20 [54]
Mild nausea	15 [40]	14 [38]
Severe nausea	6 [16]	6 [16]
Vomiting	6 [16]	4 [11]

Mean (SD) or n [%] *$p < 0.001$ between the groups.

Before discharge levels of nausea, vomiting, need for escape anti-emetic and analgesic requirements were similar in both groups.

Table 18. Outcomes before discharge.

	Cyclizine (n = 37)	Ondansetron (n = 37)
Nausea		
Mild	9 [24]	10 [27]
Severe	5 [14]	5 [14]
Nausea VAS [mm]	49 (24)	39 (26)
Vomited	5 [14]	2 [5]
PONV before discharge	14 [38]	15 [41]
Escape anti-emetic	4 [11]	5 [14]
Postoperative analgesia		
Oral	16 [43]	19 [51]
i.v.	7 [19]	9 [24]
Admission		
Nausea	1	0
Pain	1	2 [5]

Mean (SD) or n [%].

Nine patients required escape anti-emetic (cyclizine - 4; ondansetron - 5; p = ns); 1 cyclizine patient was admitted for PONV; 1 cyclizine and 2 ondansetron patients were admitted due to inadequate analgesia; 3 cyclizine and 2 ondansetron patients failed to return the postoperative questionnaire. All were omitted from the after-discharge analysis.

Table 19. Outcomes on journey home or first 24 h after discharge.

	Cyclizine (n = 32)	Ondansetron (n = 30)
Journey home		
Nausea	6 [19]	8 [27]
Vomited	0	1
Nausea after discharge		
Mild	12 [38]	7 [23]
Severe	3 [9]	5 [17]
VAS [mm]	48 (40)	42 (28)
Vomited after discharge	1	4 [13]
Total incidence PONV after discharge	14 [44]	11 [37]

Mean (SD) or n [%].

Anaesthetic times were similar in both groups, but mean (SD) time to eye opening was significantly prolonged in the group receiving cyclizine [cyclizine 10 (4) min, ondansetron 8 (2) min; p < 0.001]. However, there were no significant differences in the time to discharge between the two groups.

Comment: The comparison if there was a difference of 35% in the incidence of nausea between the groups, then the study was powered to show it, is open to being interpreted as 13/37 patients or about 7/21 patients. However the difference was only 1 patient [cyclizine, 21 (56%); ondansetron, 20 (54%)] and it was reported as p = ns, there was no testing for non-inferiority and no confidence intervals provided.

Watts SA. A randomised double-blinded comparison of metoclopramide, ondansetron and cyclizine in day-case laparoscopy. Anaesthesia & Intensive Care. 1996; 24(5): 546-551.

An initial unblinded group of 38 received no prophylactic antiemetic to assess the incidence of PONV associated with the procedure in the absence of antiemetic. This was followed by a

randomised, double-blind comparison of the efficacy of ondansetron, metoclopramide and cyclizine. Single centre; NZ.

Anaesthesia: Premedication: temazepam 10-20 mg. Induction: propofol 2-3 mg/kg after fentanyl 1.5 μg/kg. Maintenance: vecuronium 0.08 mg/kg, 50% nitrous oxide in oxygen with added isoflurane 0.5-1.0% ventilated to normocarbia. Reversal: neostigmine and atropine.
Analgesia: peri operative diclofenac 100 mg PRN; intraoperative morphine 0.18 mg/kg IV Postoperative increments of morphine IV in recovery, 10 mg IM PRN on the ward.
Inclusion criteria: women undergoing day-case gynaecological laparoscopic procedures.
Exclusion criteria: receiving opiate or antiemetic drugs in the previous 24 h; pregnant; deemed to be better served by a different anaesthetic technique; requiring more extensive surgery.
Antiemetics: According to randomisation immediately before induction, IV ondansetron 4 mg (59 patients), cyclizine 50 mg (55) or metoclopramide 10 mg (53). Rescue was prochlorperazine 12.5 mg IM.

The study objective was to assess the incidence of PONV (historical) and versus after ondansetron and metoclopramide. The primary outcome measure, the incidence of PONV, was determined by isolating patients who required treatment of their nausea or who actually had an emetic episode; this was then expressed as a percentage of the group as a whole.

The overall incidence of PONV[17] was tested using Chi-square analysis. The antiemetic groups were compared on all nausea and sedation scores using Kruskal-Wallis one-way ANOVA. The relationship between day of menstrual cycle and postoperative nausea and vomiting was tested using the Spearman Rank Correlation. Significance level for all tests was set at $p < 0.05$. The incidence result for the no antiemetic initial phase was used to determine the power necessary for the subsequent comparative trial, and showed that a sample of 160 patients would be sufficient to detect differences in efficacy between three agents with 95% confidence.

Nausea was assessed on a four-point scale:

0 = absence of PONV,

1 = mild nausea settling spontaneously,

2 = nausea requiring treatment,

3 = actual emetic episode.

Of the initial 'no antiemetic' patients, 20 had minimal or no nausea (group B), while 18 required treatment or vomited (group A). These sub-groups were comparable demographically with only past history of PONV being significantly correlated with current PONV (p = 0.0l). Overall incidence of PONV was 48%. There was a 9% overnight admission rate as a result of severe nausea or unrelenting emesis.

[17] Overall incidence of PONV was determined by isolating patients with a nausea score of 2 or greater at any time (clinically significant PONV) and this was expressed as a percentage of the group as a whole.

Table 20. Characteristics of patients enrolled in initial study.

Characteristic	GroupA*	GroupB*	*P*
n	18 (47.5)	20 (52.5)	
Age (mean)	30.7	32	
Laparoscopic Procedure:			
Tubal Ligation	10 (26)	8 (21)	NS
Dye Study	2 (5)	5 (13)	NS
Diagnostic	6 (16)	7 (18)	NS
Day of Menstrual Cycle (median)	11	14	
Past History PONV	7 (18)	0 (0)	0.01
Past History Motion Sickness	7 (18)	2 (5)	0.06
Morphine Usage (mean)	9.8	7.9	NS

Values are expressed as number of patients (%) or mean value. *Patients are divided into groups according to nausea scores returned over a 24 h study period. Group A = PONV scores ≥ 2 at any time. Group B = PONV scores ≤ 1 at all times

Table 21. Demographic characteristics of patients enrolled in the double blind comparative study.

	Ondansetron (Group O)	Metoclopramide (Group M)	Cyclizine (Group C)	*P*
n (166)	59	55	53	NS
Age (mean)	30.5 (0.74)	30.9 (0.39	30.3 (0.97)	NS
Days of Menstrual Cycle	14.5 (1.04)	14.0 (1.3)	14.8 (1.3)	NS
Phx Motion Sickness	15 (25%)	11 (20%)	15 (28%)	NS
Phx PONV	16 (27%)	11 (20%)	12 (23%)	NS
Surgical Procedure:				
Lap. Tubal ligation	31 (53%)	23 (42%)	32 (60%)	NS
Lap. + Dye	10 (17%)	6 (11%)	7 (13%)	NS
Diag. Lap.	18 (30%)	26 (47%)	14 (27%)	NS

Values are expressed as mean (plus or minus standard error of the mean; SEM) or number of patients (%) as appropriate. (Phx = past history; Lap. = laparoscopy)

The PONV scores were similar for all three groups when assessed in the recovery room and at 24 h postoperatively. There were, however, significantly lower PONV scores with metoclopramide and ondansetron at both 2 h (p = 0.008) and at discharge (p = 0.002) when compared with cyclizine.

Table 22. Postoperative nausea and sedation scores by group

	Ondansetron (Group O)	Metoclopramide (Group M)	Cyclizine (Group C)	*P*
Nausea score:				
1. Recovery	81.6	79.5	89.5	NS
2. 2 hours	74.9	80.5	96.0	0.008
3. Discharge	72.6	76.6	102.4	0.002
4. 24 hours	81.4	78.4	91	NS
Sedation Score	85.0	87.5	77.7	NS

Scores are expressed as mean rank values (Kruskal-Wallis Test).

Two ondansetron and 4 cyclizine patients were admitted overnight for severe nausea and/or vomiting.

Table 23. Incidence of clinical postoperative nausea and vomiting, overnight admission, and opiate usage by group

	Ondansetron (Group O)	Metoclopramide (Group M)	Cyclizine (Group C)	*P*
Clinical nausea	12 (20%)	13 (24%)	27 (50%)	0.03
Overnight admission	2	0	4	
Opiate requirement (mg morphine)	9.4 (0.7)	8.7 (0.7)	8.4 (0.5)	NS

Numbers are expressed as patients in each group with a PONV score ≥ 2 at any time, and opiate usage as mean morphine requirement (mg), (SEM).

Chestnutt WN and Dundee JW. The influence of cyclizine and perphenazine on the emetic effect of meptazinol. Eur J Anaesth. 1986; 3(1): 27-32.

A double-blind placebo-controlled study to compare the efficacy and safety of cyclizine and perphenazine when given in conjunction with meptazinol as preoperative medication conducted at 3 centres in the UK.

Anaesthesia: Premedication: IM 1.5 h preoperatively, 100 mg meptazinol with 50 mg cyclizine or 2.5 mg perphenazine or saline (40 patients per group). Induction: methohexitone 1.6 mg/kg. Maintenance: nitrous oxide 70% in oxygen with methohexitone PRN. Supplemented with halothane or ethrane (for 4 cyclizine and 2 placebo patients).
Analgesia: preoperative meptazinol IM.
Inclusion criteria: fit women undergoing minor gynaecological procedures.
Exclusion criteria: none given.
Antiemetics: According to randomisation 1.5 h preoperatively, IM 50 mg cyclizine or 2.5 mg perphenazine or saline. Rescue appears to be IM cyclizine 50 mg.

The study objective was the comparison of the safety and efficacy versus perphenazine and placebo. The primary outcome measures were the incidence of slight or marked nausea, vomiting (alone or with nausea). The differences between the 3 treatment groups were tested by the Kruskal-Wallis test, and the significance of the differences between pairs of treatments evaluated using a two-sample Wilcoxon test. Chi-square test was used for categorical data.

Table 24. Physical characteristics of patients (n = 40)

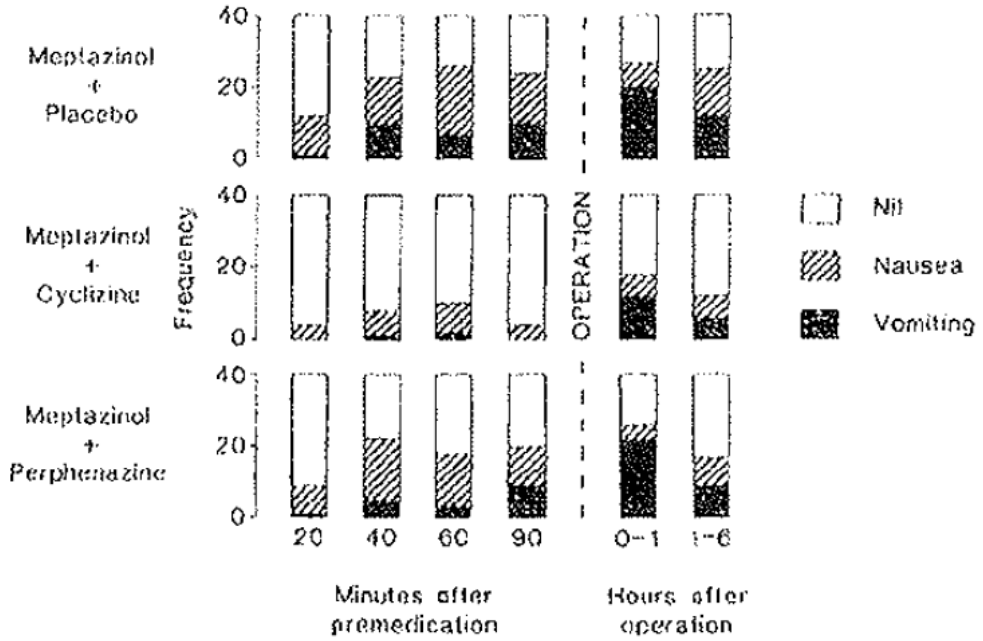
Meptazinol (100 mg) with	Age (yrs)	Weight (kg)
Saline	33 ± 11.4	61 ± 10.1
Cyclizine 50 mg	33 ± 11.0	60 ± 10.4
Perphenazine 2.5 mg	35 ± 11.4	62 ± 8.9

(mean ± SD)

Table 25. Frequency distribution of maximal emetic tendency for the pre-operative, post-operative and total study periods.

Meptazinol (100 mg) with	Pre-operative			Post-operative			Overall		
	V	N	Nil	V	N	Nil	V	N	Nil
Placebo	19	9	12	23	7	10	26	7	7
Cyclizine 50 mg	3	8	29	14	5	21	14	8	18
Perphenazine 2.5 mg	13	14	13	23	4	13	25	9	6

Figure 11. Time profile of emetic sequelae following 100 mg meptazinol administered IM as pre-anaesthetic medication for minor gynaecological procedures and accompanied by saline, 50 mg cyclizine or 2.5 mg perphenazine



The cyclizine treated group had significantly less nausea or vomiting then either the perphenazine or saline groups at all times, pre-operatively ($p < 0.001$), post-operatively ($p < 0.05$), or overall ($p < 0.01$).

Dundee JW, Loan WB, Morrison JD. A comparison of the efficacy of cyclizine and perphenazine in reducing the emetic effects of morphine and pethidine. Br J Clin Pharmac. 1975; 2(1): 81-85.

A double-blind study comparing the ability of cyclizine (50 mg) and perphenazine (2.5 and 5.0 mg) to counteract the emetic effects of pethidine (100 mg) and morphine (10 and 15 mg) in women undergoing a standard minor gynaecological operation with a standard anaesthetic. While patients were initially completely randomly allocated to the treatments toward the end of the study they were allocated to treatments by a clinician other than the investigators *"to eliminate the bias due to the powerful emetic effect of cervical dilatation per se"* by balancing *"the numbers in each group who had and who had not dilatation of the cervix uteri."* Conducted at a single centre in the UK.

Anaesthesia: Premedication: IM 1.5 h preoperatively pethidine (100 mg), or morphine (10 or 15 mg) alone or with cyclizine (50 mg) or perphenazine (2.5 mg or 5 mg). Induction and maintenance: methohexitone nitrous oxide/oxygen with no volatile agents.
Analgesia: preoperative pethidine (100 mg), or morphine (10 or 15 mg) IM. No postoperative analgesics.
Antiemetics: According to randomisation/allocation 1.5 h preoperatively, IM 50 mg cyclizine or 5 mg or 2.5 mg perphenazine. Rescue: none apparent.

Inclusion criteria: fit women undergoing minor gynaecological procedures.
Exclusion criteria: none given.
Population: 100 patients per group were intended but perphenazine 5 mg was withdrawn from the study after 50 patients because of the associated high incidence of restlessness.

Table 26. Numbers of patients in the different series studied.

Opiate	Anti-emetic			
	Nil	Cyclizine (50 mg)	Perphenazine (5 mg)	Perphenazine (2.5 mg)
Morphine (10 mg)	200	100	50	100
Morphine (15 mg)	100	100	50	100
Pethidine (100 mg)	300	100	100	100

The authors state: *"Each of the groups was broadly comparable with respect to average age and weight and duration of operation and in an analysis reported in detail elsewhere it has been shown that these are not important sources of bias in this experimental design (Morrison et al, 1968)."*

The study objective was to assess the incidence of PONV versus perphenazine and placebo. The outcome measures were the incidence of pre and postoperative nausea and/or vomiting. Details of the population calculation not provided. Details of the statistical analysis were not given, except as results.[18]

Both anti-emetics markedly reduced sickness after pethidine to a significant degree ($p < 0.0001$). The incidence of both vomiting and nausea was too low after the morphine for any statistical differences to be detected. Both cyclizine (50 mg) and perphenazine (5 mg) very significantly ($p < 0.001$) reduced postoperative vomiting and nausea in patients premedicated with morphine (10 mg). Their protective action was most marked in the first hour after operation. Morphine (15 mg) was followed by more postoperative vomiting and nausea than the 10 mg dose ($\chi^2 = 11.315$; $p < 0.001$).

All preparations studied appeared to be equally effective after the 15 mg dose of morphine as anti-emetics ($\chi^2 = 15.064$; $p < 0.0005$), but over half the patients still had some emetic sequelae. Both doses of perphenazine caused a highly significant reduction in postoperative sickness after pethidine (100 mg) and [this was] slightly more effective than cyclizine (50 mg).

The authors state: *"Under the conditions of this study both cyclizine (50 mg) and perphenazine (2.5 and 5.0 mg) were useful in countering the emetic sequelae following morphine (10 and 15 mg) and pethidine (100 mg). They appeared to act quickly as judged by the reduction in preoperative vomiting and nausea after pethidine. However, their anti-emetic effects appeared to be of much shorter duration than the emetic effect of either."*

[18] The study authors state: *"A full description of the methodology used in this long continuing series of clinical trials has been given by Dundee, Nicholl & Moore (1962)",* but this reference was not submitted.

Table 27. Incidence (%) of vomiting (V) and nausea (N) in the patients premedicated with a narcotic analgesic, with or without cyclizine (C) or perphenazine (P).

		Morphine (10 mg)				*Morphine (15 mg)*				*Pethidine (100 mg)*			
		–	*C(50 mg)*	*P(5 mg)*	*P(2.5 mg)*	–	*C(50 mg)*	*P(5 mg)*	*P(2.5 mg)*	–	*C(50 mg)*	*P(5 mg)*	*P(2.5 mg)*
Pre-op.	V	3	2	0	0	6	0	2	0	13	5	0	1
	N	9	2	6	14	11	5	14	14	31	11	12	16
	Nil	88	96	94	86	83	95	84	86	56	84	88	83
Post-op.													
0-1 h V and N		35	3	6	19	36	23	18	28	31	16	12	10
1-6 h V and N		53	23	18	43	77	45	50	49	38	15	10	13
0-6 h	V	44	9	16	34	65	37	34	38	31	13	7	8
	N	17	14	4	13	14	16	18	17	18	12	9	11
	Nil	39	77	80	53	21	47	48	45	51	75	84	81
Pre- and post-op.													
	V	46	11	16	34	65	37	34	38	34	16	7	13
	N	15	13	10	17	15	18	22	21	25	16	15	21
	Nil	39	76	74	49	20	45	44	41	41	68	78	66

Analyses performed across trials (pooled analyses and meta-analyses) – PONV

Carlisle J, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. Cochrane Database of Systematic Reviews. 3, 2006.

Selection criteria included randomised clinical trials (RCTs) that compared a drug with placebo or another drug, or compared doses or timing of administration, that reported postoperative nausea or vomiting as an outcome; including RCTs that evaluated the effect of a drug or drugs given before the onset of postoperative nausea and vomiting, but excluding studies of treatment for established postoperative nausea or vomiting and studies of anaesthetic drugs or analgesics. The drug could be given preoperatively, at induction of anaesthesia, intraoperatively or postoperatively (before nausea or vomiting had occurred), and included participants undergoing general anaesthesia, regional anaesthesia or sedation.

There were 10 studies included in the meta-analysis related to cyclizine: O'Brien *et al*., 2003; Grimsehl *et al*., 2002; Nortcliffe *et al*., 2003; Ahmed *et al*., 2000; Cholwill *et al*., 1999; Watts, 1996; Walder and Aitkenhead 1995; Chestnutt and Dundee 1986; Dundee *et al*., 1975; Hildyard *et al* 2001.

The risk for postoperative nausea and/or vomiting is decreased compared to placebo:

Table 28. Placebo versus Drug - selected agents approved or commonly used off-label for PONV.

Drug	Nausea	Vomiting	Nausea or Vomiting	Rescue antiemetic
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Cyclizine	0.65 (0.47 - 0.90)	0.57 (0.43 - 0.75)	0.68 (0.58 - 0.80)	0.27 (0.14 - 0.62)
Dexamethasone	0.57 (0.48 - 0.69)	0.51 (0.46 - 0.57)	0.49 (0.44 - 0.54)	0.50 (0.42 - 0.59
Dolasetron	0.82 (0.76 - 0.90)	0.63 (0.51 - 0.76)	0.72 (0.62 - 0.83)	0.67 (0.57 to 0.79)
Droperidol	0.65 (0.60 - 0.71)	0.65 (0.61 - 0.70)	0.62 (0.58 - 0.67)	0.53 (0.47 - 0.60)
Ephedrine	0.50 (0.20 - 1.23)	0.91 (0.64 - 1.27)	0.79 (0.55 - 1.15)	0.82 (0.41 - 1.66)
Metoclopramide	0.82 (0.76 - 0.88)	0.75 (0.70 - 0.81)	0.76 (0.70 - 0.82)	0.78 (0.69 - 0.88)
Ondansetron	0.68 (0.63 - 0.74)	0.55 (0.50 - 0.59)	0.56 (0.50 - 0.63)	0.55 (0.49 - 0.61)
Prochlorperazine	0.73 (0.56 - 0.96)	0.68 (0.52 - 0.89)	0.68 (0.55 - 0.86)	0.49 (0.22 - 1.08)
Tropisetron	0.77 (0.71 - 0.84)	0.59 (0.50 - 0.69)	0.70 (0.61 - 0.81)	0.62 (0.53 - 0.72)

Source: Cochrane 2006 review. RR – relative risk

The only cyclizine versus effective drug review result was against ondansetron.

Table 29. Effective drug versus effective drug

Drug	Nausea	Vomiting	Nausea or Vomiting	Rescue antiemetic	Differences
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	
Cyclizine – Ondansetron	1.00 (0.69 - 1.44)	1.36 (0.58 - 3.18)	1.19 (0.73 - 1.95)	0.66 (0.31 - 1.40)	0/4

Source: Cochrane 2006 review.

The authors' conclusions were that:

"Most patients given a drug to prevent nausea or vomiting after surgery will not benefit from it. Nausea or vomiting is reported to affect at most 80 out of 100 people after surgery. If all 100 of these people are given a drug, 28 would benefit, and 72 would not. Nausea and vomiting are usually less common and therefore drugs are less useful. For 100 people, of whom 30 would vomit or feel sick after surgery if given placebo, 10 people would benefit from a drug and 90 would not. Between one to five patients out of every 100 given a prophylactic antiemetic may expect to experience a mild side effect such as headache, sedation or dry mouth. There is convincing evidence that eight drugs reduce PONV by a similar amount: cyclizine, droperidol, granisetron, metoclopramide, ondansetron, tropisetron, dolasetron and dexamethasone. There is only limited evidence that more drug is more effective: there is convincing evidence that more drug is more effective for droperidol and limited evidence for dexamethasone and ondansetron. Evidence for differences in the efficacy of these eight drugs is not convincing."

The sponsor's Expert reviewer was critical of one of the studies included in the review[19] (Hildyard *et al*., 2001). Likewise the evaluator has concerns at the inclusion of two studies:

- O'Brien *et al*., 2003, where children were given an oral antihistamine premed as well as the trial drug.
- Nortcliffe *et al*., 2003, where all patients received ephedrine, morphine was given intrathecally prior to surgery and patients received cyclizine at the end of surgery.

[19] The *Clinical Summary* (Module 2.7), page 14, states: *"..the data on patients in the Hildyard et al. (2001) study were insufficient to present as pivotal data in this study. Specifically the presentation was in a non-peer reviewed Proceedings section for the..."*

Further, Walder and Aitkenhead, 1995 used cyclizine both as an IV bolus 20 min prior to the end of surgery and also as an infusion in the PCA.

Efficacy Studies - the treatment of nausea and vomiting caused by narcotic analgesics

The supporting evidence for this indication is based on 3 studies using single dose IM premedication where patients were observed for only 90 min (see above for study descriptions) and one study using oral opiate and oral cyclizine.

Chestnutt and Dundee, 1986

The cyclizine treated group had significantly less nausea or vomiting than either the perphenazine or saline groups pre-operatively ($p < 0.001$).

Table 30. Frequency distribution of maximal tendency for the pre-operative study period.

	Pre-operative		
Meptazinol (100 mg) with	V	N	Nil
Placebo	19	9	12
Cyclizine 50 mg	3	8	29
Perphenazine 2.5 mg	13	14	13

Dundee et al, 1975

Cyclizine markedly reduced sickness after pethidine to a significant degree ($p < 0.0001$). The incidence of both vomiting and nausea was too low after the morphine for any statistical differences to be detected.

Table 31. Percentage incidence of vomiting (V) and nausea (N) in the patients premedicated with a narcotic analgesic, with or without cyclizine (C) or perphenazine (P).

		Morphine (10 mg)				*Morphine (15 mg)*				*Pethidine (100 mg)*			
		–	*C(50 mg)*	*P(5 mg)*	*P(2.5 mg)*	–	*C(50 mg)*	*P(5 mg)*	*P(2.5 mg)*	–	*C(50 mg)*	*P(5 mg)*	*P(2.5 mg)*
Pre-op.	V	3	2	0	0	6	0	2	0	13	5	0	1
	N	9	2	6	14	11	5	14	14	31	11	12	16
	Nil	88	96	94	86	83	95	84	86	56	84	88	83

Dundee JW, Halliday F, Nicholl RM, Moore J. Studies of drugs given before anaesthesia. X. Two non-phenothiazine anti-emetics--cyclizine and trimethobenzamide. Br J Anaesth. 1966; 38(1): 50-57.

This study was similar to Chestnutt and Dundee 1986 and Dundee *et al*., 1975 in methodology except that it was not blinded for the combination of cyclizine and pethidine. Cyclizine significantly decreased ($p < 0.05$) the incidence of pre-operative vomiting associated with pethidine.

Table 32. Details of subjects and average duration of operation.

Premedication	No. of cases	Average age (yr)	Average weight (kg)	Average duration of anaesthesia (min)
Atropine 0.6 mg plus				
Nil	300	34.7	59.5	8.7 ± 0.24
Cyclizine 50 mg	50	32.1	56.1	6.2 ± 0.36
Trimethobenzamide 200 mg	60	32.4	58.8	8.5 ± 0.44
Pethidine 100 mg plus				
Nil	200	32.3	60.8	7.3 ± 0.25
Cyclizine 50 mg	100	31.4	57.8	6.2 ± 0.47
Trimethobenzamide 200 mg	100	30.2	58.6	7.1 ± 0.32

Table 33. Observations before anaesthesia, after pre-anaesthetic medication had been given.

	Atropine 0.6 mg plus			Pethidine 100 mg plus		
	—	Cyclizine 50 mg	t.m.b. 200 mg	—	Cyclizine 50 mg	t.m.b. 200 mg
Emetic effects						
Nausea	2	4	0	34	11	18
Vomiting	0	0	2	12	5	1

Atropine or pethidine were given alone or in combination with cyclizine 50 mg and trimethobenzamide (t.m.b.) 200 mg as indicated. Results are expressed as percentage.

Dundee and Jones, 1968

The trial was intended as a double blind sequential study of the effect of cyclizine on the nausea and vomiting produced by a variety of opiates and placebo. The authors state:

"Already established regimes of analgesics were continued and combined with either 50 mg cyclizine or an identical placebo tablet, irrespective of the dose of analgesic. It was frequently possible to try several equipotent analgesics on the same patient at intervals of several weeks, thus increasing the number of available observations".

"Where it was ethically permissible, because of lack of severity of the pain, placebos resembling each of the analgesics in the trial were also used. In some instances the emetic effect of these had been tested prior to starting the full trial. Patients who became nauseated or vomited after the placebo are referred to as 'placebo readers' in the results."

"It was originally planned that each patient would take the active anti emetic drug and the inert placebo for either three or seven days, depending on whether they were to return to the clinic in one or two weeks time. Since they were always given a supply of tablets in excess of their requirements in a few cases, where the beneficial effects of the cyclizine were marked, this drug was taken for a longer period of time than the placebo.

An essential part of the organization of this trial was the dispensing of all drugs directly to the patients on their attendance at the out-patient clinic, rather than giving them a prescription. They were supplied with a written set of instructions as to the dosage and frequency of administration of each drug, each preparation being referred to by a number and letter, A and B being used in random order for cyclizine and the placebo. The patient's co-operation was assured by explaining that it was 'up to himself to find which treatment suited him best'. Each patient in the trial was asked to complete a questionnaire which recorded daily the analgesia anti side-effects of the drugs."

Table 34. The effect of cyclizine on incidence (%) of emetic effects in all patients.

Variables Analysed	No. of Cases	Percentage of Cases Experiencing Symptoms when receiving: NO CYCLIZINE: Nausea and Vomiting	NO CYCLIZINE: Nausea* only	CYCLIZINE: Nausea and Vomiting	CYCLIZINE: Nausea* only	Relief produced by Cyclizine: Nausea and Vomiting	Relief produced by Cyclizine: Vomiting	Relief produced by Cyclizine: Nausea* only
All patients	83	66	27	55	53	22	97	26
Sex								
Males	38	66	27	50	50	24	100	30
Females	45	67	29	60	56	20	94	23
Causes of Pain								
Malignancy	33	73	24	64	64	13	100	25
Neuralgias	16	63	25	44	38	40	100	50
Others	34	62	33	53	50	24	90	18
Age								
Under 60	48	75	25	63	59	19	96	8 -
Over 60	35	54	31	46	46	26	100	45

* Apparent discrepancy is due to patients who vomited without Cyclizine and who had nausea only when the anti-emetic drug was given.

Table 35. Comparison of the protective action of cyclizine against analgesic induced nausea and vomiting in patients who were nauseated by placebo (positive response) and in those in whom the placebo had no such effect.

	Positive		Negative	
Total Nausea without Cyclizine	43/50	86%	67/169	40%
Total Nausea with Cyclizine	44/50	88%	36/169	21%
Total Nausea and Vomiting Relief*	3/43	7%	35/67	52%
Significance of Effects of Cyclizine			$\chi^2 = 13.42$ $P < 0.001$	
Nausea only, relief with Cyclizine	3/19	16%	16/31	52%
Vomiting, without Cyclizine	24/50	48%	36/169	21%
Vomiting with Cyclizine	16/50	32%	6/169	4%
Vomiting relief*	16/24	66%	33/36	92%
Significance of Effects of Cyclizine	$\chi^2 = 2.66$ $0.20 > P > 0.10$		$\chi^2 = 24.44$ $P < 0.01$	

* Apparent discrepancy is due to patients who vomited without Cyclizine and who had nausea only when the anti-emetic drug was given.

The authors further state:

> *"The table shows the incidence of nausea and vomiting without cyclizine to be twice as high in the positive placebo group as in the other. It is interesting to note that while the placebo reactions themselves are mild, this does not influence the severity of nausea due to analgesics; in both groups about 55 per cent of those who were nauseated at all did actually vomit. Relief by cyclizine is virtually confined to the negative placebo reaction group."*

The evaluator has concerns about (a) the validity of the results in that there is some evidence of abuse/withdrawal that could have produced a desire to report nausea or vomiting where none was occurring; and (b) the studies' applicability to the proposed formulation which requires injection.

Efficacy Studies - Pre-operative use in patients undergoing emergency surgery to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia

The sponsor's *Summary of Clinical Efficacy* did not discuss this [proposed] indication. In the sponsor's *Clinical Overview* it is stated:

"Cyclizine has demonstrated a significant effect on lower oesophageal pressure. Intravenous cyclizine 25 mg given intravenously to volunteers increased the mean barrier pressure from by an average of 1.87 kPa to 3.29 kPa (P < 0.005) (Brock-Utne et al., 1977). This has been seen as of particular benefit in patients undergoing emergency surgery.

The superiority of cyclizine compared to other agents in the prevention of vomiting in emergency surgery has not been demonstrated clinically and comparisons of meaningful clinical studies are unlikely to be conducted due to the nature of the clinical situation. Apart from the clinical difficulty of recruitment of patients in this emergency situation the ethical obstacles appear to be unsurmountable due to the difficulties in obtaining fully informed consent in this situation and other issues of study conduct. "

Thus no evidence has been produced or is likely to be produced to support the claim of efficacy in reducing the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia.

There is evidence (Brocke-Utne *et al*., 1977, 1978; see section on *Pharmacodynamics*, above) that in healthy volunteers the basal barrier (due to sphincter) pressure increased with cyclizine. This may decrease the risk of regurgitation in the awake emergency patient. There was no evidence provided that this protection persists on induction of anaesthesia.

Evaluator's conclusions on clinical efficacy for post-operative nausea and vomiting

Dent *et al*., 1954 in relation to vomiting wrote *"With the advent of new anaesthetic drugs and associated alteration in techniques of administration, the incidence of this complication has been reduced."*

The balance of evidence for efficacy of the proposed dosage and administration used in post operative nausea and vomiting is favourable with Cholwill *et al*., 1999 (42 patients), Chestnutt and Dundee, 1986 (40 patients) and Dundee *et al.*, 1975 (300 patients) showing significant effect compared to placebo; while Grimsehl *et al.*, 2002 (37 patients) claimed they showed no significant difference from ondansetron. Dundee *et al*., 1966[20] did show an incidence of PONV after atropine only premed fell from 55 to 25% but the difference was not significant. Watts, 1996 (59 patients) showed no effect compared to placebo (overall 50% versus 48%).

Only the studies by Cholwill *et al*., 1999 and Watts, 1996 used muscle relaxants. Chowill reversed them with neostigmine and glycopyrrolate, while Watts reversed with neostigmine and atropine: this may account for the differences in results.

All these 5 studies used only a single dose of 50 mg of cyclizine IM or IV except Chestnutt and Dundee, 1986, where 2 patients received a second dose of cyclizine.

While the studies were all of short duration procedures, they were gynaecologic procedures, mostly in women of child bearing age, and including nitrous oxide, major risk factors. Indeed the anaesthetics and procedures are generally considered a good model for testing for emesis in relation to surgery. Unfortunately, other than Dundee's (1975) study the numbers involved are small. Details of all studies' statistical analyses were published, but that for Dundee *et al*., 1975 was not submitted.

Evaluator's conclusions on clinical efficacy for the treatment of nausea and vomiting caused by narcotic analgesics

The balance of evidence for efficacy of the proposed dosage and administration used in the treatment of nausea and vomiting caused by narcotic analgesics is favourable with Chestnutt and Dundee, 1986 and Dundee *et al*., 1975 showing significant effect compared to placebo; although Dundee *et al*., 1966 did so as well, it was essentially an open study. These were studies only for 1.5 h before anaesthesia was added. Dundee *et al*., 1975 stated: *"anti-emetic effects appeared to be of much shorter duration than the emetic effect of either* (morphine or pethidine)*."* There were no

[20] Not fully evaluated.

studies of repeat dosing for this indication. Thus the evaluator has concerns in relation to repeated use.

Evaluator's conclusions on clinical efficacy for pre-operative use in patients undergoing emergency surgery

No evidence has been produced or is likely to be produced to support the claim of efficacy in reducing the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia. In healthy volunteers the basal barrier (due to sphincter) pressure is increased with cyclizine.

Safety

Studies providing evaluable safety data

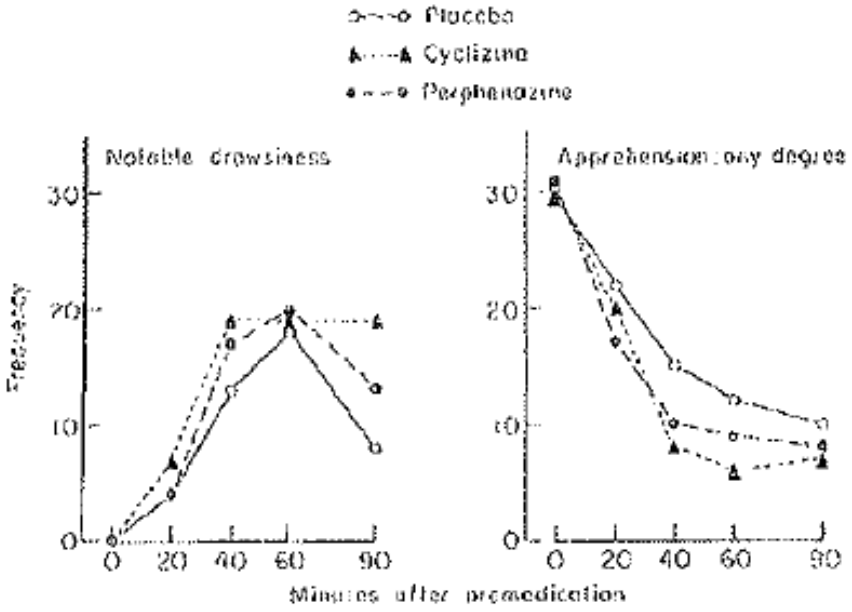
Safety data from efficacy studies considered pivotal by the evaluator are summarised below.

Cholwill *et al*., 1999: No safety data.

Chestnutt and Dundee, 1986: at 90 mins preoperatively, cyclizine patients were significantly more ($p < 0.01$) drowsy than those who had received placebo. Apprehension decreased with time and there was no significant difference between treatments at any time point. There was no clinically significant restlessness in any group of patients. The incidence of marked dizziness was 5/40 for placebo and 3/40 for cyclizine patients.

The presence of dry mouth was reported after treatment by 14 patients in the placebo group, and 28 patients in the cyclizine group. When the occurrence of this symptom, before treatment, is accounted for there is no significant difference between the groups. Nine patients in the placebo group and 15 in the cyclizine group reported blurring of vision but there was no significant difference between the groups. None of the premedication regimes had a clinically significant effect on the cardiovascular system.

Figure 12. Frequency of notable drowsiness (i.e. moderate or marked) or apprehension of any degree at the time intervals of the preoperative study period, following 100 mg meptazinol accompanied by saline, 50 mg cyclizine or 2.5 mg perphenazine.



Dundee *et al*., 1966: Dizziness, a frequent complication with cyclizine, was always mild and transitory. Cyclizine increased the frequency of excitatory phenomena to a significant ($p < 0.001$) degree when pethidine was not given, but no such increase was found when it was combined with pethidine pre-anaesthetic medication.

The increased incidence of excitatory phenomena and the high average total dose of methohexitone following the use of cyclizine can be attributed to its moderate antanalgesic action as described by Nicholl *et al.*, 1962. This may be correlated with the frequency with which poor conditions of anaesthesia followed the use of this premedicant; a further reason is thus provided for advising against its pre-operative use without analgesics.

The soporific effects of both anti-emetics are again evident when they were combined with pethidine (see Table 36, below). In the case of cyclizine this has been noted by Bonica *et al.*, 1958 and Blatchford 1961; whilst Moore *et al.*, 1956 recommended that, for this reason, doses of routine premedication drugs should be reduced when it is intended to combine them with cyclizine

While cyclizine 50 mg reduced the frequency of preoperative dizziness noted following pethidine, this symptom is still complained of by one-third of all patients; this is an unacceptably high incidence.

Pethidine and cyclizine required two syringes and two injection sites.

Table 36. Observations before anaesthesia, after pre-anaesthetic medication had been given. Atropine or pethidine were given alone or in combination with cyclizine 50 mg and trimethobenzamide (t.m.b.) 200 mg as indicated.

	Atropine 0.6 mg plus			Pethidine 100 mg plus		
	—	Cyclizine 50 mg	t.m.b. 200 mg	—	Cyclizine 50 mg	t.m.b. 200 mg
Drowsiness						
Good	4	12	17	28	49	47
Fair	10	24	15	45	37	38
Slight	31	34	35	20	13	10
Apprehension						
Slight	29	36	42	26	8	32
Moderate	13	18	13		4	5
Marked	11	18	7			2
Restlessness or excitement	9	16	3	2	1	3
Pain at injection site	7	7	13	2	1	8
Dizziness	7	30	7	59	34	32
Emetic effects						
Nausea	2	4	0	34	11	18
Vomiting	0	0	2	12	5	1
Tachycardia (beats/min)						
100–120	42	28	22	16	16	33
121–140	7	10	2	6	1	2
141+	5	14	3	0	1	1
Hypotension	1	8	3	4	7	7
Efficacy score 1	20	28	7	4	1	3
2	40	24	42	12	3	3
3	27	30	31	28	18	17
4	10	12	15	35	32	46
5	3	6	5	21	46	31
Mean	2.36	2.44	2.70	3.57	4.19	3.99
Toxic score 1	43	28	67	24	49	36
2	40	44	23	22	31	34
3	13	22	8	32	11	28
4	3	4	0	16	4	1
5	1	2	2	6	5	1
Mean	1.79	2.08	1.31	2.58	1.85	1.97
Mean net score	+0.57	+0.36	+1.39	+0.99	+2.24	+2.02

Results expressed as percentage.

Table 37. Course of anaesthesia as shown by average dose of drugs, frequency of complications, and state of consciousness 2 minutes after discontinuation of nitrous oxide-oxygen anaesthesia (from Dundee *et al*., 1966)

	Atropine 0.6 mg plus			Pethidine 100 mg plus		
	—	Cyclizine 50 mg	t.m.b. 200 mg	—	Cyclizine 50 mg	t.m.b. 200 mg
Average dose of metho-hexitone (mg/kg)						
Induction	1.57	1.60	1.58	1.56	1.59	1.53
Total	2.24 ± 0.04	2.92 ± 0.07	2.38 ± 0.11	2.14 ± 0.05	2.05 ± 0.04	2.15 ± 0.07
Course of anaesthesia						
% excitatory phenomena	33	60	28	6	1	12
% respiratory upset	26	36	28	42	28	23
% hypotension (fall 20 mm Hg +)	13	17	20	14	7	9
Grade of anaesthesia						
% 1 (uneventful)	51	28	50	49	65	64
% 2a (slight upset)	32	34	36	37	31	20
% 2b (moderate upset)	13	12	6	12	4	16
% 3 (very troublesome)	4	26	8	2	0	0
Condition 2 min after end						
% awake	77	48	60	43	64	48
% safe	22	40	32	44	30	31
% unsafe	1	12	8	13	6	21

Dundee, 1975: Restlessness was not observed with cyclizine.

Dundee and Jones, 1968: No safety data.

Grimsehl *et al*., 2002: When given IV, cyclizine has been shown to cause sedation and this may be of relevance in the day-case setting. It was demonstrated that the patients in the cyclizine group had a significantly longer time to eye opening than the ondansetron group ($p < 0.001$). There was no difference, however, in the time to discharge between the two groups.

Watts, 1996: This study failed to demonstrate any difference between any of the agents following analysis of sedation scores. No dystonic side-effects or major adverse reactions were recorded for any of the trial agents. One patient who received cyclizine developed localized erythematous rash.

Safety data from the non-pivotal efficacy studies

Johns R.A, Hanousek J, Montgomery J.E. A comparison of cyclizine and granisetron alone and in combination for the prevention of postoperative nausea and vomiting. Anaesthesia. 2006; 61(11): 1053-1057.

With regard to side-effects, significantly more women who were given cyclizine complained of drowsiness but this did not affect their recovery in terms of unplanned admissions. The side-effects that were analysed in this study were considered to be those most commonly suffered by patients being given the two drugs used according to clinical practice and the data sheet for each drug. However, it is very difficult to draw any meaningful conclusions as to the direct relationship between the side-effects and the use of these drugs because of the large number of confounding factors such as anaesthesia itself, the fluids given, the type of surgery and the use of opioids. This study was not powered to analyse each of these factors independently and in detail.

Table 38. Side-effects that could be attributed to the anti-emetics used in the study.

	Cyclizine *n* = 316	Granisetron *n* = 322	Cyclizine-granisetron *n* = 322	p value
Dizziness	126 (40%)	102 (32%)	129 (40%)	0.04
Drowsiness	176 (56%)	144 (45%)	174 (55%)	0.005
Headache	42 (13%)	49 (15%)	45 (14%)	0.79

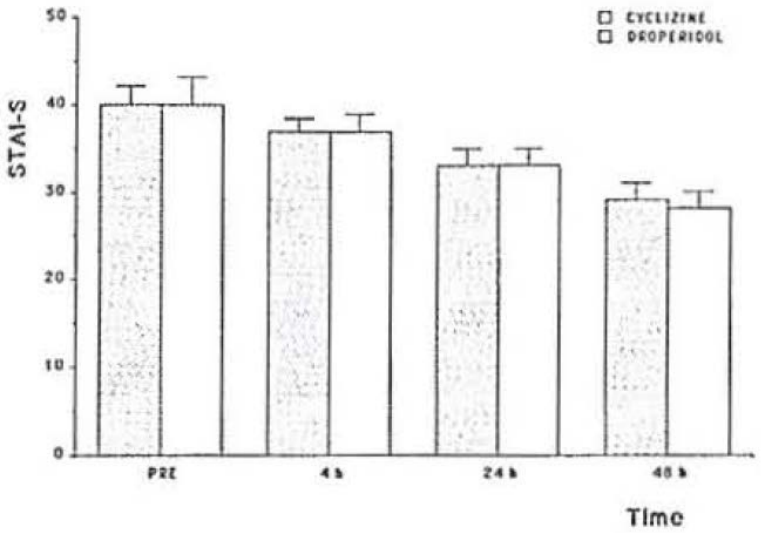
Values are number (%).

Laffey and Boylan JF Cyclizine and droperidol have comparable efficacy and side effects during patient-controlled analgesia. Irish J Med Sci. 2002; 171(3): 141-144.

Postoperative period: No overt dysphoria or extrapyramidal symptoms occurred. State Trait Anxiety Inventory [STAI; a widespread method of measuring pre-operative anxiety for research] scores decreased over time ($p < 0.001$) to a similar extent in each group. Mini mental state (MMS) scores were decreased at 4 h relative to baseline and later post-operative scores ($p < 0.0001$) but were comparable in both groups throughout. Scores in the Trieger dot test (where individuals are asked to connect a series of 50 dots of a geometrical figure) did not differ between groups at any time points.

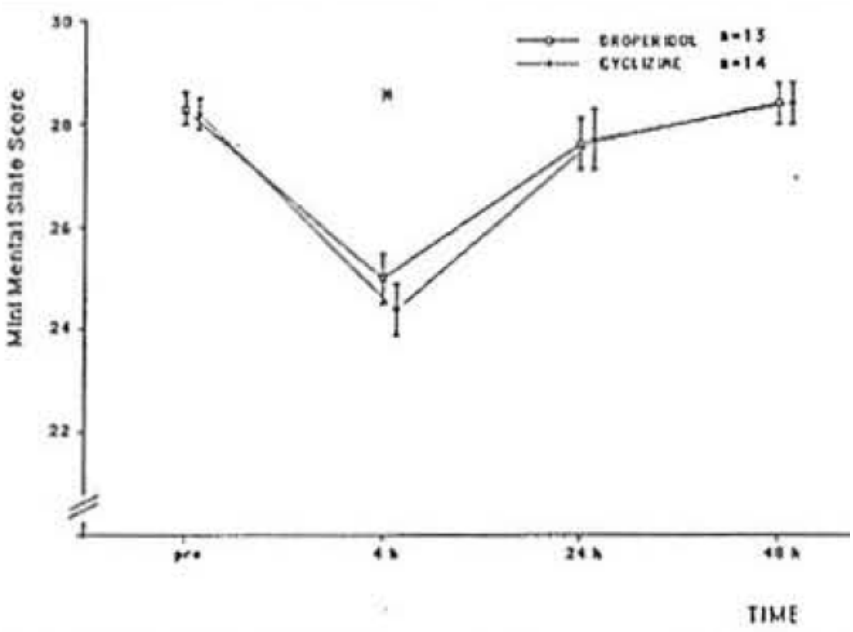
Patient sedation, psychomotor performance and anxiety levels were similar with both antiemetic agents. Anxiety levels decreased significantly over time in both groups. The authors state: *"With a 'number needed to treat' value of 3 we felt unable for ethical reasons to use placebo controls."*

Figure 13. STAI scores. State anxiety decreased comparably over time in both groups.



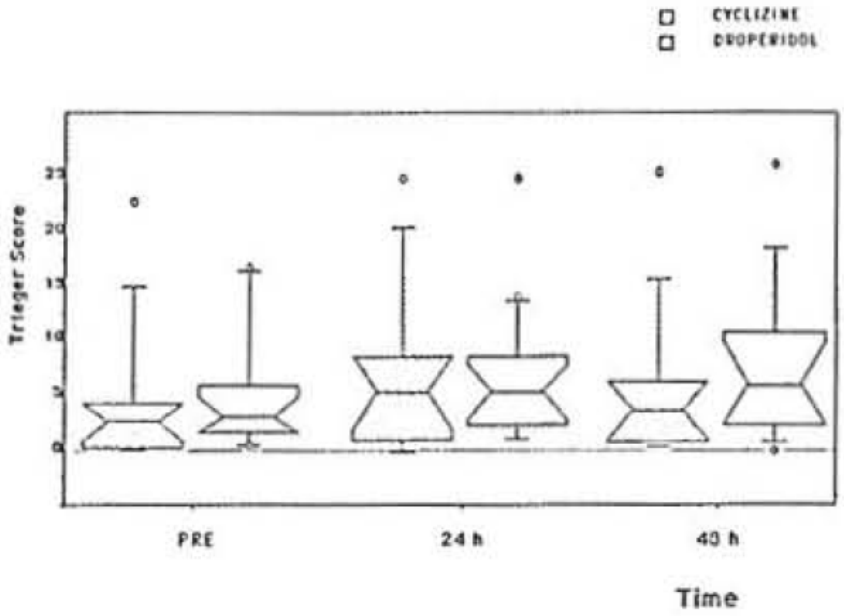
Data are mean (plus or minus standard error of the mean; SEM).

Figure 14. MMS scores. MMS scores decreased at 4 h postoperatively relative to pre-operative scores in both groups.



Data are mean (SEM). ·p < 0.01.

Figure 15. Notched box plots depicting Trieger dot test scores. Values were similar for both group 5 at all time points.



Data are medians (plus or minus inter-quartile range; Q1-Q3).

Moore DC, Bridenbaugh LD, Piccioni VF, Adams AP, Lindstrom CA. Control of Post Operative Nausea and Vomiting: A Double-Blind Study. Anesthesiology. 1956; 17: 690-695.

The authors reported that: *"no tissue necrosis occurred following the parenteral administration of MAREZINE [cyclizine lactate solution]. Burning, the prevalence of which forced us to discontinue the injection of MAREZINE when it was first tried in 1953, caused only an occasional complaint during this study. Perhaps this is explained by the care which was taken in this series to avoid the inadvertent placement of the solution subcutaneously, since it had been suggested that too superficial a placement of this drug might have been responsible for the burning…. To date, we have seen no reactions other than an occasional case of drowsiness"*.

Nortcliffe SA, Shah J, Buggy DJ. Prevention of postoperative nausea and vomiting after spinal morphine analgesia for caesarean section: comparison between cyclizine, dexamethasone, and placebo. Br J Anaesth. 2003; 90(5): 665-670.

Systolic arterial pressures (SAP), ventilatory frequency, and sedation were all clinically unremarkable and also not significantly different between the groups. The data showed no evidence of increased sedation in patients receiving cyclizine compared with dexamethasone or placebo.

Table 39. Pain, adverse effects and overall satisfaction with antiemetic therapy.

	Cyclizine (C) (*n*=30)	Dexametha-sone (D) (*n*=30)	Placebo (P) (*n*=30)
Overall VAS satisfaction with Postoperative care (mm)	78 (50–100)	58 (25–85)*	51 (20–75)**
Pain VAS highest	2.0 (0–5)	2.4 (1–5)	2.6 (0–5)
Pain VAS lowest	0.5 (0–3)	1.0 (0–3)	0.8 (0–4)
Incidence pruritus, *n* (%)	23 (77)	25 (83)	25 (83)
Pruritus highest score	1.5 (0–3)	1.5 (0–3)	1.5 (0–3)
Sedation highest score	0.6 (0–2)	0.2 (0–1)	0.3 (0–1)
SAP highest, mm Hg	112 (21)	114 (12)	115 (18)
SAP lowest, mm Hg	106 (11)	108 (18)	106 (20)
Ventilatory frequency/min lowest	18 (2)	17 (2)	16 (1)

Mean (SD), median (range) or number (%) as appropriate. *p = 0.03, C vs. D; **p = 0.008, C vs. P
VAS=visual analogue scale for pain or patient satisfaction with postoperative care, as indicated.

O'Brien C.M. Titley G. Whitehurst P. A comparison of cyclizine, ondansetron and placebo as prophylaxis against postoperative nausea and vomiting in children. Anaesthesia. 2003; 58(7):707-711.

Pain on injection was recorded only in those receiving cyclizine ($p < 0.001$). No arrhythmias were recorded with ondansetron and normal saline, but one patient (of 50) developed a nodal tachycardia following administration of cyclizine.

Walder AD and Aitkenhead AR. A comparison of droperidol and cyclizine in the prevention of postoperative nausea and vomiting associated with patient-controlled analgesia. Anaesthesia. 1995; 50(7): 654-656.

There were no significant differences in pain, sedation, or nausea scores between the groups. Three patients in group 1 (droperidol) and one in group 2 (cyclizine) reported feelings of anxiety and agitation which improved when the PCA was discontinued. One patient in group 2 reported blurred vision immediately postoperatively, this resolved spontaneously after 30 min.

Other studies evaluable for safety only

Brand, J.J, Colquhoun W.P and Perry, W.L.M Side effects of L-Hyoscine and Cyclizine studied by objective tests. Aerospace Med. 1968; 39(9):999-1002.

Cyclizine 15 and 100 mg PO had no effect on salivation, pulse rate, vision, or mental performance (arithmetic).

Tan LB, Bryant S, Murray RG. Detrimental haemodynamic effects of cyclizine in heart failure. Lancet. 1988; i: 560:1.

Cyclizine significantly increased systemic and pulmonary arterial pressures, and right and left ventricular filling pressures, and negated the venodilatory effects of diamorphine. The use of cyclizine in patients with heart failure should, therefore, be avoided.

Case studies that assessed safety

- **Back and Taubert, 2007:** Akathisia and an unusual symptomatic treatment
- **Collier 1986:** Agranulocytosis associated with oral cyclizine responded to discontinuation.
- **Dagg and Wrathall, 2003:** Dystonic reaction to cyclizine.

- **Griffiths and Peachy, 1970:** Fixed drug eruption– erythema, irritation and inflammation.
- **Kew *et al*., 1973:** Hypersensitivity hepatitis.
- **King *et al*., 2003** Probable dystonic reaction after a single dose of cyclizine in a patient with a history of encephalitis.
- **Klawans and Moskovitz, 1977:** Cyclizine induced chorea.
- **Marr and Orvin, 2006:** Transient paralysis after administration of cyclizine.
- **Michailidou and Peck, 2004:** Dystonic reaction to cyclizine.
- **Russell, 1969:** Cyclizine anaphylaxis, when administered with propanidid.
- **Sandhu *et al*., 2005** Transient paralysis after administration of a single dose of cyclizine, two cases.
- **Sewell and Nixon, 2003:** Dystonic reaction to cyclizine. The female developed generalised choreiform movements, which lasted for approximately 20 min. Her reaction was reported to the manufacturer of Valoid (cyclizine). The authors reported that *"In the previous 10 years, they [the sponsor] had 40 reports of uncoordinated muscle movements associated with cyclizine. ..They classify this side-effect as rare… These uncoordinated muscle movements are variously described: dystonia, twitching, facial twitching, choreiform movements, chorea, extrapyramidal effects, jerky movements, tremor, orofacial dyskinesia, dyskinesia, hyperkinesia, hyperreflexia, muscle spasm, muscle rigidity and muscle hypertonia."*

Pivotal studies that assessed safety as a primary outcome

Not Applicable.

Patient exposure

For the period 1 April 1996 to 31 January 2010 the total number of Valoid ampoules sold was 37,877,560. The injections may be given up to three times a day but in many cases just a single dose is given to patients undergoing operation. The number of daily doses administered in this period is in excess of six million.

Adverse events

All adverse events (irrespective of relationship to study treatment)

Adverse events in the literature that are reported in the proposed PI include:

Drowsiness, sedation, dizziness, blurring of vision, headache, excitatory phenomena, chorea, dystonic reaction, transient paralysis, dry mouth, localized erythematous rash, fixed drug eruption – erythema irritation and inflammation, anaphylaxis, agranulocytosis, and tachycardia.

Those not in the proposed PI were:

Anxiety (reported in Walder and Aitkenhead, 1995).

Akathisia (reported in Back and Taubert, 2007).

Treatment-related adverse events (adverse drug reactions)

See above.

Deaths

None reported in literature.

Serious adverse events

Serious adverse events (SAEs) reported in the literature include:

Dystonic reaction (5), transient paralysis (3), and 1 each of drug eruption, anaphylaxis, agranulocytosis, and hypersensitivity hepatitis.

Discontinuation due to adverse events

Many of the study reports were of a single dose so that despite an SAE, there was no discontinuation. AEs leading to discontinuation include:

One each of anaphylaxis, agranulocytosis, dystonic reaction, feelings of anxiety and agitation.

Laboratory tests

None reported in literature.

Post-marketing experience

The first PSUR was 1 April 1991 to 31 March 1996; written by Glaxo Wellcome the original Marketing Authorisation Holder. Amdipharm submitted 3 PSURs, for the periods:

- 1 April 1996 to 31 October 2004,
- 1 November 2004 to 30 June 2008,
- 1 July 2008 to 31 January 2010.

PSUR 1st April 1996 to 31st October 2004

218 reports (471 events), 121 SAEs. 169 parenteral, 90 IV, 18 IM, 5 SC, 20 PO.

Six reported deaths with limited associated information.

A 45 year old female patient developed necrotising fasciitis after a single day's treatment with cyclizine injection.

Table 40. Summary of AEs (PSUR April 1996 to October 2004)

BODY SYSTEM	DESCRIPTION
Cardiac (23)	Atrial fibrillation (1); Coronary artery disease aggravated (1); Heart block (1); Palpitations (2); QT interval prolonged (1); Tachycardia (17)
Congenital (2)	Congenital gastrointestinal malformation (1); Congenital musculoskeletal malformation (1)
Ear & Vestibular (1)	Hearing loss (1)
Eye (13)	Anisocoria (1); Eye abnormality (1); Eye discharge (1); Eye inflammation (1); Glaucoma (1); Miosis (2); Ocular swelling (1); Vision abnormal (1); Vision blurred (3); Visual field defect (1)
Gastrointestinal (15)	Abdominal pain (3); Dry mouth (2); Nausea (4); Retching (1); Tooth discolouration (1); Tooth erosion (1); Vomiting (3)
General & administration site (47)	Abscess (1); Asthenia (2); Chest pain (1); Chest tightness (1); Death – cause unknown (2); Drug abuse (1); Drug interaction (1); Drug maladministration (2); Injection site erythema (1); Injection site haematoma (1); Injection site necrosis (3); Injection site pain (3); Injection site paraesthesia (1); Injection site pruritus (1); Injection site reaction (10); Malaise (6); Peripheral oedema (1); Phlebitis (4); Pyrexia (2); Rigors (1); Thrombophlebitis (2)
Hepato-biliary (9)	ALT increased (1); Cholestatic hepatitis (1); Hepatic function abnormal (2); Hepatic function abnormal aggravated (1); Hepatitis (2); Jaundice (2)
Immune system (8)	Allergic reaction (3); Anaphylactic reaction (5)
Injury & Poisoning (3)	Overdose (3)
Investigations (8)	Blood pressure increased (1); Creatine phosphokinase increased (1); Decreased oxygen saturation (4); Hypokalaemia (2)
Musculoskeletal (23)	Fasciitis (1); Joint stiffness (1); Muscle disorder NOS (1); Muscle flaccidity (1); Muscle hypertonia (1); Muscle hypotonia (2); Muscle ridigity (5); Muscle spasm (7); Myositis (1); Necrotising fasciitis (1); Torticollis (2)
Nervous system (176)	Ataxia (1); Burning sensation (2); Cerebral dysfunction (1); Chorea (2); Collapse (1); Consciousness decreased (12); Consciousness increased (1); Convulsions (5); Convulsions tonic-clonic (2); Convulsions aggravated (2); Convulsions grand mal (2); Decreased appetite (1); Dizziness (14); Drowsiness (5); Dyskinesia (2); Dysphasia (1); Dystonia (21); Encephalitis (2); Extrapyramidal disorder (3); Faintness (4); Footdrop (1); Hypothermia (1); Headache (3); Hyperreflexia (2); Malignant hyperpyrexia (1); Lack of co-ordination (1); Lightheaded feeling (3); Lip smacking (1); Loss of consciousness (8); Nerve paralysis (1); Nystagmus (2); Oculogyric crisis (4); Opisthotonos (1); Pain limb (3); Pain NOS (1); Paraesthesia (8); Paralysis vocal cords (1); Relaxation (1); Restless limbs (1); Seizure in known epileptic (1); Speech disorder (23); Syncope (1); Tetany (1); Tremor (12); Twitching (6); Unsteady gait (2); Vertigo (1); Wrist drop (1)
Pregnancy (4)	Foetal death in utero (1); Premature baby (2); Stillbirth (1)
Psychiatric (64)	Agitation (4); Amnesia (2); Confusion (27); Crying (1); Delirium (1); Delusion (1); Depression (1); Disorientation (7); Euphoria (1); Feeling detached (1); Feeling strange (1); Hallucinations (8); Mental alertness increased (1); Mood elevation (2); Nervousness (1); Psychosis (1); Restlessness (1); Schizophrenia aggravated (1); Sleep disorder (1); Suicide attempt (1)
Reproductive (1)	Undescended testicle (1)
Respiratory (30)	Airway obstruction (1); Apnoea (3); Breath holding (1); Breathing difficulty (2); Breath shortness (2); Bronchospasm (3); Burning pharynx (1); Cyanosis (3); Dyspnoea (3); Hiccup (2); Hyperventilation (3); Laryngospasm (1); Pulmonary congestion (1); Respiratory arrest (1); Respiratory depression (1); Respiratory rate decreased (1); Tachypnoea (1)
Skin & subcutaneous tissue (22)	Angioneurotic oedema (2); Erythema (2); Face oedema (1); Pallor (1); Pruritus (2); Rash (3); Rash erythematous (3); Rash papular (1); Rash pruritic (1); Rash vesicular (1); Skin discolouration (1); Skin scarring (1); Sweating increased (2); Urticaria (1)
Vascular (22)	Flushing (5): Hypertension (11); Hypotension (6)

PSUR 1 November 2004 to 30 June 2008

Table 41. Summary of AEs (PSUR November 2004 to June 2008)

System Organ Class	Total AE	Serious Adverse Events		Non-Serious Adverse Events	
		Unlisted	Listed	Unlisted	Listed
Infections and infestations	**3**	3	0	0	0
Immune system disorders	**9**	0	9	0	0
Metabolism and nutrition disorders	**2**	2	0	0	0
Psychiatric disorders	**54**	16	36	1	1
Nervous system disorders	**171**	38	102	3	28
Eye disorders	**24**	11	8	2	3
Ear and labyrinth disorders	**1**	1	0	0	0
Cardiac disorders	**31**	11	18	0	2
Vascular disorders	**30**	12	11	4	3
Respiratory, thoracic and mediastinal disorders	**25**	19	3	3	0
Gastrointestinal disorders	**32**	18	13	1	0
Hepatobiliary disorders	**1**	0	1	0	0
Skin and subcutaneous tissue disorders	**37**	11	18	2	6
Musculoskeletal and connective tissue disorders	**18**	10	5	0	3
Renal and Urinary Disorders	**1**	0	1	0	0
Pregnancy, peurperium and perinatal conditions	**5**	4	0	0	1
Reproductive system and breast disorders	**2**	2	0	0	0
General disorders and administration site conditions	**56**	33	9	3	11
Investigations	**15**	7	8	0	0
Injury, poisoning and procedural complications	**16**	3	3	1	9
Surgical and medical procedures	**2**	2	0	0	0
TOTAL	**535**	**203**	**245**	**20**	**67**

See Appendix I for a list of AEs by Preferred Term.

PSUR 1 July 2008 to 31 January 2010

It was recommended that the European Summary of Product Characteristics (SmPC) be updated to include the statement that *'rapid IV administration can lead to symptoms similar to overdose'*.

Table 42. Summary of AEs (PSUR July 2008 to January 2010).

System Organ Class	Total AE	Serious Adverse Reactions		Non-Serious Adverse Reactions	
		Unlisted	Listed	Unlisted	Listed
Immune system disorders	**3**	0	3	0	0
Psychiatric disorders	**19**	12	4	0	3
Nervous system disorders	**43**	14	24	1	4
Eye disorders	**2**	0	1	0	1
Cardiac disorders	**5**	1	1	0	3
Vascular disorders	**4**	2	2	0	0
Respiratory, thoracic and mediastinal disorders	**3**	2	1	0	0
Gastrointestinal disorders	**3**	3	0	0	0
Skin and subcutaneous tissue disorders	**5**	2	3	0	0
Musculoskeletal and connective tissue disorders	**4**	4	0	0	0
Pregnancy, puerperium and perinatal conditions	**2**	1	0	0	1
General disorders and administration site conditions	**14**	5	0	4	5
Investigations	**5**	1	2	1	1
Injury, poisoning and procedural complications	**12**	2	0	2	8
TOTAL	**124**	**49**	**41**	**8**	**26**

See Appendix II for a list of AEs by Preferred Term.

Specific safety issues of regulatory importance

Liver toxicity

None reported in literature.

Haematological toxicity

Agranulocytosis.

Serious skin reactions

None reported in literature.

Injection site reactions

Moore *et al.*, 1956 reported seeing none in that study but referred to seeing it previously. O'Brien *et al.*, 2003 reported that pain on injection (IV) was recorded only in those receiving cyclizine ($p < 0.001$). It is possible that IM injections have their sensation modified by the drug's local anaesthetic properties.

It is reported in the 1996-2004 PSUR:

> *"There were six reports of phlebitis/thrombophlebitis and three of injection site necrosis. Other reports described pain, erythema, inflammation, vein tracking and stinging or*

burning sensations. A single report of abscess involved subcutaneous infusion into the upper arms over a period of three weeks. A further nine reports of injection site reactions were included in the previous PSUR.

It is possible that some of these cases may have been a consequence of administration of Valoid with saline-containing solutions. Cyclizine has a pH of 3.3-3.7, and is known to be incompatible with solutions with a pH of 6.8 and above. Any solution with significant concentrations of chloride ions, including normal saline, may lead to the precipitation of the less soluble cyclizine hydrochloride."

Two reports of AEs associated with **long-term use** of cyclizine injection:

- A 38-year-old female on cyclizine IM three times daily (TDS) for five years developed lesions on the legs; biopsy showed fasciitis and myositis. Serum creatinine kinase was elevated
- A male with terminal cancer on IM Valoid 50 mg for some months reported that the injection had caused damage to the muscles around the site of injection. The patient described the event as necrosis and reported that he had to undergo surgical removal of the dead tissue from the arm.

Cardiovascular safety

Significantly increased systemic and pulmonary arterial pressures and right and left ventricular filling pressures in patients with heart failure.

Unwanted immunological events

Agranulocytosis.

Other safety issues

Use in Pregnancy

The relevant references are listed in Table 43, below. The evaluator has concerns at accepting the data from McBride 1969, 1963.

The studies only looked at congenital anomalies. While cyclizine is more likely to be used in early pregnancy the possibility of withdrawal symptoms in the neonates of mothers using it late in pregnancy does not appear to have been considered. In the absence of the data from McBride, there were in the submission only 111 pregnant patients who were reviewed after taking cyclizine. Additional data was contained in the paper by Asker *et al.,* 2005, which was provided on request from the TGA.

Milkovich *et al*., 1976:

While the results contain no signal for cyclizine the study contained only 111 patients who had taken cyclizine, and the standard error (of the mean) for the *Severe congenital anomaly* (SCA) rate at 5 years was comparatively high.

Table 43. Severe congenital anomaly (SCA) rates* for children at ages 1 month, 1 year, and 5 years according to the nausea and vomiting (N/V) complaints of their mothers and the drugs prescribed for the complaints within 84 days from their last menstrual period (LMP)

Nausea and vomiting (N/V) status	No. of mothers with single live births	SCA rate per 100 children at ages			Standard error for SCA rate at 5 years
		1 month	1 year.	5 years	
Total	10,205	1.5	2.4	3.5	0.18
N/V of pregnancy	6,305	1.6	2.5	3.4	0.23
Cyclizine	111	1.8	1.8	3.7	1.82
No drug prescribed for N/V	4,353	1.5	2.2	3.2	0.27
No N/V of pregnancy					
Medical record stated no N/V	1,564	1.4	2.4	3.8	0.39
Medical record contained no statement	2,336	1.4	2.8	3.7	0.34

Table 44. SCA rates per 100 live births at 1 month, 1 year, and 5 years of age for children, according to the drug and to the gestational time in pregnancy that the mother was prescribed the drug for N/V of pregnancy.

SCA rates according to type of drug prescribed	*Date of last menstrual period (LMP) to date drug prescribed (days)*				
	Total (1-84)	*1-42*	*43-56*	*57-70*	*71-84*
Cyclizine	111	10	36	37	28
SCA rate at age					
1 mo.	1.8	0.0	2.8	0.0	3.6
1 yr.	1.8	0.0	2.8	0.0	3.6
5 yr.	3.7	0.0	2.8	0.0	3.6

Table 45. Peri natal death rates* and peri natal deaths and severe congenital anomaly (SCA) rates combined according to gravida's nausea and vomiting (N/V) status and the drugs prescribed for N/V within the first 84 days of pregnancy.

Nausea and vomiting status	*Live births and fetal deaths ≥20 wk.*	*Rates/1,000 for exposed risk*	
		Perinatal deaths	*Perinatal deaths and SCA*
All gravidas	10,441	35.2	66.3
N/V of Pregnancy	6,432	30.8	60.2
Drugs prescribed for N/V	1,981	27.8	60.1
Cyclizine	112	17.9	53.6
No drug prescribed for N/V	4,451	32.1	60.2
No N/V of Pregnancy	4,009	42.2	76.1
Medical record stated no N/V	1,599	41.9	75.7
Medical record contained no statement	2,410	42.3	76.3

*Fetal deaths at 20 weeks and neonatal deaths.

Table 46. Summary of all submitted studies relevant to pregnancy. Table continued across two pages.

Reference	Details and relevant findings.	Comments
Collins, 1964	Review. Based on animal data, not recommended in early pregnancy. No evidence of fetal damage - quoting Mellin *et al.*,1963	-
McBride, 1963	Reported an incidence of congenital abnormalities of 0.1% in 6,000 deliveries of women who had taken cyclizine, from a total of 21,562 deliveries over 5years 1957-1962 • congenital heart disease, 5 • cleft palate and/or hare-lip, 5 • anencephaly, 1 • myeloencephalocele, 2 • hydrocephalus, 1 • bilateral cataract, 1	Part of nonclinical submission
McBride, 1969	Reported an incidence of cleft palate of 0.4% in 1,125 deliveries of women who had taken cyclizine in the first 3 months from a total of 25,333 deliveries over 6 years 1956-61 Incidence among mothers with nausea and vomiting who did not take cyclizine was 3.64% of 1,100 deliveries (no significant difference) Incidence among mothers who did not take cyclizine was 0.08% of 24,208 deliveries. (significantly different from those with N/V suggesting N/V was the cause)	Not in nonclinical submission
Mellin *et al.*, 1963.	Of 266 babies with malformations, no mothers had taken cyclizine.	Letter Part of nonclinical submission

Reference	Details and relevant findings.	Comments
Milkovich L and van den Berg, 1976	Human incidence. While the results contain no signal for cyclizine the study contained only 111 patients who had taken cyclizine, and the standard error for the *Severe congenital anomaly* rate at 5 years was comparatively high.	Precautions Not in nonclinical submission
Sadusk *et al*., 1965	Is in list of references for the sponsor's *Clinical Summary,* but paper is only in nonclinical dossier. The report of the findings of a Food and Drug Administration (FDA) committee that on the basis of lack of evidence recommended insertion [on product labelling] of the following statements, and review in 2 years. *"The following information should be taken into account in determining whether the potential benefits of ... (cyclizine, meclizine, chlorcyclizine) . . . outweigh the risks of its use in women of childbearing age and particularly during pregnancy. A review of available animal data reveals that this drug exerts a teratogenic response in animals such as the . . . (rat, mouse, rabbit, or dog). While available clinical data are inconclusive, scientific experts are of the opinion that this drug may possess a potential for adverse effects on the human foetus. Consequently, consideration should be given to initial use of a non phenothiazine agent that is not suspected of having a teratogenic potential. In any case, the dosage and duration of treatment should be kept to a minimum.* *The effectiveness of these drugs for the prevention and treatment of nausea and vomiting of pregnancy has not been established, and the decision to use such drugs should be based upon the seriousness of the situation, remembering that while these drugs have been used clinically for a decade, there are yet no controlled studies to demonstrate usefulness in an objective fashion. In most cases, nausea and vomiting of pregnancy may be unpleasant but does not present a serious threat to the health of the patient or to the progress of her pregnancy. In view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, management by physiologic means such as proper nutrition and by psychological support is preferable to antiemetic drug therapy."* The results of the subsequent review were not submitted.	- Part of nonclinical submission
Yerushalmy and Milkovich, 1965	Not related to cyclizine.	Part of nonclinical submission

Some PSURs contained relevant information:

PSUR 1 April 1996 to 31 October 2004

Of 10 exposed in pregnancy 7 had no obvious congenital defects (1 was later diagnosed with 80% hearing loss in one ear); 3 had congenital abnormalities (all different).

The Medicines and Health Care Regulatory Agency (MHRA) Committee on Safety of Medicines (CSM) Drug Analysis Print for cyclizine contains fourteen reports of congenital

anomalies, including the three cases presented within this report. Three reports of alimentary tract anomalies (duodenal atresia, imperforate anus, oesophageal atresia), five of limb deformities and single cases of ear malformation, cataract, cleft lip, micrognathia, renal agenesis and cryptorchism have been received by the CSM since 1964.

PSUR 1 November 2004 to 30 June 2008

Asker *et al*., 2005 analysed the Swedish Medical Birth Registry to define the use of anti-emetics during pregnancy and the outcome of the pregnancies. During the period July 1 1995 to 2002, 29,804 pregnant women with 31,130 infants reported the use of antiemetic drugs from a total of 665,572 pregnant women with 676,198 infants that were registered.

Table 47. Reported use of cyclizine and the period of pregnancy during which the drug was taken (from Asker *et al*., 2005)

	Period of reported drug use[a]			
Drug	First trimester	Second to third trimester	First to third trimester	Total
Cyclizine	1,221	460	337	2,018

[a] First trimester means that prior use of the drug was reported during the first antenatal visit (usually before week 12); second to third trimester means that the drug was prescribed after the first antenatal visit; first to third trimester means that prior use of the drug was reported during the first antenatal visit and an antiemetic was prescribed during subsequent antenatal care.

Table 48. Preterm birth, low birth weight, small-for-gestational age and congenital malformations* according to cyclizine use (from Asker *et al*., 2005)

	Group	Number	Percentage	OR[a]	95% CI[a]
Preterm birth	Population	33,653	5.1	1.00	Reference
	Cyclizine	97	4.7	1.01	0.87–1.16
Low birth weight	Population	21,086	3.2	1.00	Reference
	Cyclizine	47	2.3	0.81	0.65–0.99
Small-for-gestational age	Population	14,247	2.2	1.00	Reference
	Cyclizine	32	1.6	0.84	0.59–1.20
Congenital malformations	Population	23,745	3.5	1.00	Reference
	Cyclizine	79	3.6	1.08	0.86–1.35

[a] Odds ratios (OR) with 95% CI, adjusted for year of birth, maternal age, parity, smoking, and years of involuntary childlessness. * Registered in the Medical Birth Registry among all infants born.

Extracted from Asker *et al*., 2005: *"The registered malformation rate varies for the different drugs, with 3.6% for cyclizine being the highest. However, this variability may be random (chi-square = 4.9 at 6 df , p = 0.56). Many of the registered malformations are mild conditions and have not been registered uniformly; for example, coloboma of the eye, preauricular tags, branchial cysts or fistulas, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicle, unstable hip, and skin malformations (mainly naevus). After these mild conditions are removed from the analysis, 684 infants with malformations remain in the antiemetic-exposed group (2.2%) and 16,994 in the population (2.5%). The adjusted OR remains at 0.90 (95% CI 0.83–0.97). The use of all sources for congenital malformations gave a better ascertainment and also identified malformations observed after the neonatal period – 4.7% of all infants born have a recorded congenital malformation on this basis. Among infants exposed to antiemetics, the rate is 4.3% and the crude OR is 0.93 (95% CI 0.88–0.98). This material was used in order to identify specific groups of congenital malformations. The ORs vary between the different groups, but a chi-square analysis indicates that the*

heterogeneity has only a marginal statistical significance (chi-square = 14.1 at 7 df, p = 0.049). Hypospadias, however, shows intrinsically a significantly low OR.

The register also has weaknesses. It is unlikely that all drug use is reported or recorded. In this study, about 5% of all women reported the use of antiemetics during pregnancy. In a questionnaire study from a region of Sweden, 15% of the women reported the use of drug treatment of NVP and about 13% reported the use of antihistamines. The lower rate in the present study may not only be due to a lack of reporting/recording but also to the fact that women after the first antenatal care visit may use over-the-counter drugs which will not be registered. However, the incomplete identification of women who used antiemetics will only slightly influence the risk estimates because the relatively few unidentified cases will only marginally dilute statistics of the large control population. Another draw-back of the register is that little information is available on the timing or duration of drug use or the amount taken. Data for women who only used a single tablet is confounded with data for women who used drugs for an extended period. This tends to bias the estimated ORs towards unity.

No information is obtainable for spontaneous or induced abortions. According to present Swedish law, induced abortions cannot be registered with personal identification data, which makes it impossible to study such cases for, among other things, drug use. A number of abortions will have been induced because of congenital malformations detected during prenatal diagnosis and will not be included in the analysis. While this will scarcely affect the risk estimates, it will reduce the power of the study. If the malformation in question is always or nearly always aborted (like anencephaly or bilateral kidney agenesis), obviously a possible teratogenic effect of the studied drugs cannot be identified. If the use of a drug (e.g., anticonvulsant) can affect the probability or degree of a detailed prenatal diagnosis, biased results can be obtained. It is very unlikely that the use of antiemetics will have such an effect."

Safety related to drug-drug interactions and other interactions

Cyclizine is sedative, and CNS depression with other sedatives is expected. Because of its anticholinergic activity, cyclizine may enhance the side-effects of other anticholinergic drugs.

Abuse and addiction

There were a number of literature reports of abuse and addiction. The distinction between recreational abuse, intentional overdose and inadvertent overdose was not always clear.

Table 40. Summary of all submitted studies relevant to abuse and addiction. Table continued across two pages.

Therapeutically initiated	
Bailey and Davies, 2008	IV cyclizine 4 cases Rapid injection buzz (high for 30 – 120 mins) Mostly psychological but some physical withdrawal symptoms (feeling sick and achy) Potentiation of stimulant effects of opioids hallucinations with higher doses Abuse produces aggression and seizures
Hughes and Coote, 1988.	Dependence with withdrawal in chronic pain patients Case reports (3)
Recreational abuse - oral preparations – ingested or injected	
Ruben *et al*., 1989.	20 opiate addicts on oral methadone, habitual abusers of cyclizine, were interviewed. The effects initially were of

	intense stimulation, often with hallucinations, sometimes with aggressive behaviour, and occasionally with epileptic fits. Subsequent depressive mood changes occurred often accompanied by a craving for cyclizine
Bassett *et al*., 1996.	Reviewed 80 teenage cases of abuse reporting to the Utah Poisons Centre (of whom only 25% had co ingestions), 52% had tachycardia (> 115 beats/min), 69% had systolic hypertension (> 135 mmHg), 15% had diastolic hypertension, and 14% had fever (> 38^{o}C). The most commonly reported symptom was hallucinations, noted in 70% of cases. Other reported symptoms included confusion or disorientation in 40%, agitation in 31 %, tremor in 9%, dysarthria in 7%, drowsiness in 5%, ataxia in 2%, chest pain in 1 %, and seizures in 1 %. Ingestion was considered to have been secondary to abuse in 89% of cases, suicide attempt in 4%, misuse in 2%, and intentional/unknown in 5%.
Turnbull and Isaacson, 1977.	Case study, injection of dissolved oral tablets
Williams *et al*., 1997.	Not in submission. Subsequently submitted on request from TGA. Dipianone HCl (an opiate) plus cyclizine injection of dissolved oral tablets 86 patients current intravenous abusers. There was a mortality rate of 3%.
Accidental Overdose	
Haidvogl and Rosegger, 1975.	6 cases of accidental overdose in infants. Symptoms included agitation – ataxia, sleeplessness, visual and acoustic hallucinations, confused orientation, febrile, facial reddening, wide pupils.
Overdose not otherwise specified (NOS)	
Resch *et al*., 1982.	Abstract only submitted (later translated): 38 cases reviewed of 128 reports to poisons centre of intoxication with cyclizine in adults and children. Use of gastric lavage and physostigmine recommended.
Griffin and Baselt, 1984.	The cyclizine blood concentration of 450 ng/mL reported in the drowning death of an actress probably represents more than normal usage of this drug. In acute fatal overdoses involving cyclizine, much higher blood concentrations (1.5 to 15 µg/mL have been observed

Overdose in children

Resch *et al.,* 1982 report the following in relation to children:

"The toxic dose, i.e. the dose, which causes at least some of the clinical symptoms described below, is 5mg/kg body weight in our patient collective.

The first sign of intoxication is usually an unapparent state of excitation with an increased urge to move, tremors, athetoid patterns of movement, ataxia, rigidity, stereotypes and other hyperkinetic extrapyramidal manifestations, with there being no record of any definite dose or age dependency with regard to intensity and nature of motor agitation.

The hyperkinesias can escalate to tonic-clonic seizures, with children and adolescents especially showing an increased disposition for this, while in the age group over 16 years at

appropriate doses no seizures are described in any documented case, in our experience children aged between 5 – 16 years develop convulsions in around 70 % of cases. No real dose-dependency can be derived for the occurrence of seizures, however it becomes evident that, from a dose of 40 mg/kg body weight, a clustering of convulsions to over 60 % are also observed in the infant age group. The convulsive states can sometimes take on a threatening aspect and lead to respiratory insufficiency with cyanosis, as was the case in 6 of our patients.

In over 70 % of cases in infants, following consumption of more than 40mg/kg cyclizine, and in schoolchildren up to even 100 %, a range of central and peripheral atropine-like symptoms are found, with hallucinations, confusion, temporal and spatial disorientation on the one hand and clear facial reddening, dry skin, mydriasis and tachycardia on the other hand. Dry mucosa and phonation disorder, described as typical in the context of atropine intoxication, can only be detected in one case.

A phase of central depression is associated with the excitation phase and, in rare cases, can dominate the clinical symptoms. There is no definite age dependency, yet it is revealed that in the group of 5-16 year olds dose-dependent signs of sedation, disorientation, somnolence to the point of coma are to be found in 85 % of cases, i.e. more frequently than in the other age groups. In contrast to earlier publications, in our experience central depressive effects of cyclizine also become manifest in infancy in over 50 %.

There is no actual prognostic sign. Only one out of all cases was recorded as fatal, and in fact following a complicated course with aspiration pneumonia, constant convulsive states and apnoea during a seizure on the 5th day. This child had taken the highest oral dose, 88.8mg/kg body weight, of all known intoxication cases."

Evaluator's overall conclusions on clinical safety

The most common adverse reaction in the trials is sedation/drowsiness. This is so for most of the trials involving anaesthesia with and without opiate premedication, an effect noted with most antihistamines. The oral trials also found it common but mostly subjective.

Pain on injection was noted in the earlier IM studies as well as IV in children. In the latter study (O'Brien *et al*., 2003) pain occurred despite an antihistamine premedication.

Many of the reported adverse events are those that would be expected given the central anticholinergic mode of action of the drug. They are well described by Resch *et al*., 1982 in overdose in children. Together with the absence of a multiple dose pharmacokinetic trial or pharmacokinetic modelling with a drug whose half life exceeds the proposed dosing interval, it suggests the possibility of a narrow therapeutic index, especially with repeated dosing.

The potential for abuse and the possibility of addiction are of concern.

The odds ratio for congenital malformations of 1.08 is of some, but not great concern (the confidence intervals cross 1.0). No data was available on the possibility of withdrawal symptoms in the neonates of mothers using cyclizine late in pregnancy.

Preliminary benefit-risk assessment and recommendations

Preliminary assessment of benefits

The treatment of nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period

The benefits of cyclizine in the proposed usage are:

- Efficacy was demonstrated in the studies.

- PONV has a better response to multimodal therapy and cyclizine appears in part to act to modify vestibular function (but at 100 mg orally).
- The drug has a long history of use for this indication.
- Long term use is not covered by the indication.

Pre-operative use in patients undergoing emergency surgery

The benefits of cyclizine in the proposed usage are:

- Both cyclizine and metoclopramide increased barrier pressure significantly, thus confirming previous reports indicating that these two drugs increase lower oesophageal sphincter tone
- It is a single 25 mg dose use.

Preliminary assessment of risks

The treatment of nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period

The risks of cyclizine in the proposed usage are:

- The evidence of efficacy is limited in that
    - the studies for PONV essentially used only a single dose of 50 mg of cyclizine IM or IV
    - and those on opiates alone were studies only for 1.5 h before anaesthesia was added.
- Only 2 studies used muscle relaxants: 1 showed efficacy, 1 did not, and different agents were used for reversal of the muscle relaxation.
- The absence of a multiple dose pharmacokinetic trial or pharmacokinetic modelling with a drug whose half life exceeds the proposed dosing interval suggests the possibility of a narrow therapeutic index, especially with repeated dosing.
- The drug can cause pain on injection.
- Long term use can cause muscle damage.
- The drug has a low pH that may lead to incompatibilities.

Pre-operative use in patients undergoing emergency surgery

The risks of cyclizine in the proposed usage are:

- No evidence has been produced or is likely to be produced to support the claim of efficacy in reducing the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia.
- There is evidence (Brocke-Utne *et al*., 1977, 1978; see section on *Pharmacodynamics*) in healthy volunteers that the basal barrier (due to sphincter) pressure increased with cyclizine. This may decrease the risk of regurgitation in the awake emergency patient but it does not necessarily follow that it does so on induction of anaesthesia.
- The evidence is not good in that the studies by Brocke-Utne *et al*., 1977 and 1978 appear to be duplicate reports.

Preliminary assessment of benefit-risk balance

The benefit-risk balance of cyclizine for the treatment of nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period, is favourable

given the age the drug has been in the market, however the lack of long term studies and appropriate pharmacokinetic data restrict its use, possibly to single dosing.

The benefit-risk balance of cyclizine for pre-operative use in patients undergoing emergency surgery to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia is unfavourable.

Preliminary recommendation regarding authorisation

The evaluator recommended that the application for registration of cyclizine on the Australian Register of Therapeutic Goods (ARTG) be approved with the modified indications of:

- the prevention and short-term treatment of nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period
- pre-operative use in patients undergoing anaesthesia and surgery to increase lower oesophageal sphincter pressure where this is required.

List of questions

Safety

In Dundee *et al*., 1966 the authors comment:

"The only real advantage of trimethobenzamide over cyclizine was its miscibility with pethidine; doses of pethidine 100 mg and trimethobenzamide 200 mg were prepared premixed in 2-ml ampoules, whereas, as stated previously, pethidine and cyclizine required two syringes and two injection sites."

From the 1996-2004 PSUR:

"Cyclizine has a pH of 3.3-3.7, and is known to be incompatible with solutions with a pH of 6.8 and above. Any solution with significant concentrations of chloride ions, including normal saline, may lead to the precipitation of the less soluble cyclizine hydrochloride."

The evaluator recommended the sponsor provide compatibilities with common infusions used in anaesthesia, for example IV fluids, propofol, muscle relaxants, opiates.

Sponsor's response: The sponsor's response contained the warning

"..if cyclizine lactate injection must be diluted for use in a syringe driver, the drug should be diluted with water for injection or 5% dextrose injection

Interaction with propofol or muscle relaxants (both of which may be given by infusion) is unknown.

Some strengths of oxycodone resulted in precipitation[21] This was the only Australian marketed opiate for which there was information.

Compatibility with 50 mg/5mL ranitidine was shown (there is also a 50 mg/5 mL marketed."

The evaluator recommended that the *Dosage and Administration* section of the PI carry appropriate warnings.

V. Pharmacovigilance findings

Risk management plan

The summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

[21] Trissel LA. Handbook on Injectable Drugs, Cyclizine Lactate. American Society of Health System Pharmacists® 12th Ed (in section 31 response)

There are some possible safety concerns with Valoid which the Applicant believes have been appropriately addressed in the PI and the intended post-authorisation communications.

These concerns are:

- Off-label use
- Paediatric use
- Rapid administration of injection
- Use in pregnant women
- Hypotensive patients in emergency surgery
- Product abuse

OPR reviewer comment

Pursuant to the evaluation of the nonclinical and clinical aspects of the safety specifications, it is recommended that 'injection site reactions' be added to the list of Potential safety concerns.

Pharmacovigilance plan

The sponsor provides the information that the pharmacovigilance system of Link Medical Products will be incorporated into the Amdipharm (UK and Ireland licence holder) pharmacovigilance system. The sponsor provides a detailed description of the pharmacovigilance activities to be undertaken routinely.

The sponsor does not propose any additional pharmacovigilance activities.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The sponsor notes in the RMP Section *Post-marketing (non-study) exposure* that the database only contains 390 case reports. The sponsor has explained that although the product has been on the market for 50 years Amdipharm has held the licence since 1 December 2003 and that the ADR case reports are for the time period 1 December 2003 to 31 August 2011. The sponsor has provided complete case line listings and a frequency table for review. In addition the sponsor has provided the MHRA Drug Analysis Print (DAP) for all cyclizine cases for the period 1 July 1963 to 27 July 2011 containing the Council for International Organizations of Medical Sciences (CIOMS) forms for all 760 cases.

Risk minimisation activities

In the detailed action plan for specific safety concerns the sponsor states that the safety concerns raised within the RMP have been accounted for with warnings in the PI and intended communications. The sponsor believes this strategy is adequate to address the risks associated with this product.

OPR reviewer comment:

The sponsor has indicated, following a TGA request for information, that there will be additional materials provided with the launch of the product that will focus on the PI. The sponsor has not provided sample material for comment. Therefore the adequacy of the material to address the safe administration of Valoid cannot be evaluated. The sponsor is requested to provide a copy of this material to the TGA, for information, post registration.

The sponsor indicates that changes in spontaneous adverse event reporting will be used as an indicator of the effectiveness of the communication.

Given the small number of adverse events reported for cyclizine, and the sponsor's argument for the relative safety of cyclizine in many of its potential off-label indications in Australia, it is suggested that spontaneous adverse event reporting is unlikely to a useful tool for the evaluation of the post-authorisation communications. A drug utilisation study may provide a better profile of the use of the product in the community post registration.

In regard to the proposed routine risk minimisation activities, changes to the proposed PI are recommended.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to reflect any changes to the PI.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; and the implementation of the RMP (undated, version not identified) and the sponsor's responses to TGA requests for information, is imposed as a condition of registration when so qualified:

Risk minimisation plan

The sponsor has indicated that there will be additional materials provided with the launch of the product that will focus on the PI. The sponsor has not provided sample material for comment. Therefore the adequacy of the material to address the safe administration of Valoid cannot be evaluated. The sponsor is requested to provide a copy of this material to the TGA, for information, post registration.

Given the small number of adverse events reported for cyclizine, and the sponsor's argument for the relative safety of cyclizine in many of its potential off-label indications in Australia, it is suggested that spontaneous adverse event reporting is unlikely to a useful tool for the evaluation of the post authorisation communications to prevent off-label use. A drug utilisation study may provide a better profile of the use of the product in the community post registration.

Product Information

Suggested revisions to the proposed PI were recommended. Inclusion of these is beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections in respect of Chemistry, Manufacturing and Controls to registration of this product.

The quality evaluator had stated that approval could not be recommended until the company developed a suitable method for monitoring the finished product and generates appropriate stability data. The sponsor has now developed a suitable method and provided the appropriate stability data.

No bioavailability data for the injection when administered by the IM route were submitted.

This submission was discussed at the PSC at its August 2011 meeting. The PSC saw no quality or pharmaceutical aspects which would preclude registration: the PSC endorsed all the questions raised by the TGA in relation to quality and pharmaceutic aspects of the

submission and considered all outstanding issues should be addressed to the satisfaction of the TGA.

Nonclinical

The nonclinical evaluator considered that based on current regulatory guidelines and GLP standards required for nonclinical studies to support registration of a new chemical entity, the nonclinical dossier was not adequate. The nonclinical data used to demonstrate primary pharmacodynamic efficacy were limited to one study (from 1954) that documented an antiemetic effect by cyclizine in an experimental model of emesis, with little/no data presented that explored the dose-dependency, efficacy, selectivity and/ or mode of action. Limited experimental data showed antihistamine but not anticholinergic activity.

Cardiovascular and central nervous systems were (minimally) investigated in safety pharmacology studies but no ECG or hERG assays were performed. In rats oral cyclizine at doses above 75 mg/kg/day was associated with pancreatic pathology and plasma glucose/insulin changes. Metabolism was studied only in dogs (a species not used for any of the toxicity tests) and it is unknown whether the potential toxicity of human metabolites was assessed in the animal studies.

Repeat dose toxicity was limited to a 12 week dietary study in rats. The primary human metabolite, norcyclizine had negligible antihistaminic properties. Cyclizine inhibited human hepatic estrone sulfotransferase and murine MAO-B but showed only weak inhibition of human CYP2D6 and 2C9.

Genotoxicity assessment was limited to one Ames test in which mutations were seen only when cyclizine was in a nitrosated form. The nonclinical evaluator considered this may be relevant for oral administration if nitrites are present in food. There were no carcinogenicity studies, but this could be accepted if the medicine was used only for short periods.

Published reproductive toxicity studies examined oral cyclizine administration in rats, mice and rabbits during gestation. There was evidence of resorptions and malformations in all species. NOEL values were not consistent across the variable study designs.

There was no evidence of maternal toxicity. Placental transfer, excretion into milk, and maternal exposure measurements were not assessed.

In view of the above issues, the nonclinical evaluator considered that clinical evaluation was needed for assurance that the identified nonclinical deficiencies are adequately offset by sufficiently well-documented clinical information.

Clinical

Pharmacology

Only one single dose study of the pharmacokinetics of cyclizine was submitted. This was of a bolus IV dose of 25 mg cyclizine, given as 0.5 mL of 50 mg/mL solution to 6 subjects. Concentration/time data were also available from one subject given a single oral 50 mg dose and one subject given a single 50 mg intravenous dose. No pharmacokinetic data were available for the proposed intramuscular route of administration.

Data from the pharmacokinetic study are summarised in Table 1 of this AusPAR.

Published papers have stated that cyclizine is primarily metabolised by demethylation to norcyclizine or by glucuronidation. Renal clearance is negligible.

The submission included some papers published in the 1950s that considered aspects of the pharmacodynamic effects of cyclizine. Effects on the vestibular apparatus were

examined with results suggesting that a 50 mg dose would have minimal suppressive effects on visual-vestibular interaction. There is good evidence that in overdose cyclizine is associated with tachycardia, systolic and diastolic hypertension and fever. These are well-known effects of antihistamine overdose.

Two studies by the same authors (Brocke-Utne *et. al*.) published in the 1970s examined the effect of single 25 mg doses of cyclizine given intravenously to healthy, awake volunteers. Oesophageal sphincter pressure increased from a basal mean of 19.1 cm H_2O to 33.5 cm H_2O ($p < 0.005$). It is not clear if these studies were in fact the same study of the same patients or if different patients were enrolled in studies of the same design with similar results.

A dose of 50 mg of cyclizine, given IV to 11 patients with severe heart failure (New York Heart Association grade 4) was associated with raised ventricular filling pressures and an increase in after-load. This was accompanied by a reduction in cardiac output. These events could lead to reduction of coronary artery flow and increase in myocardial oxygen consumption which could be compromising in patients with severe cardiac failure.

Efficacy

The dose chosen for the efficacy studies appears to have been based on historical use rather than from Phase II efficacy/safety studies. The evaluator has noted that anaesthetic techniques have changed considerably over time. Consequently the techniques reported in the submitted papers may no longer be regularly used and historical data on the incidence of nausea and vomiting associated with various types of surgery may not be relevant. However, comparative data where patients in each group received similar anaesthetics with and without cyclizine may be evaluable for efficacy. All the presented studies used either PO or parenteral doses of 50–100 mg cyclizine.

The sponsor requested indications for the *prevention and treatment* of nausea and vomiting including A) that caused by narcotic analgesics and by general anaesthetics in the post-operative period and B) pre-operative use in emergency surgery to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia.

Most of the evidence presented was for prevention of PONV. Treatment of established PONV was not specifically assessed. To support that PONV component of the proposed indications a Cochrane systematic review of drugs for preventing PONV and 12 studies were presented.

The Cochrane review *Drugs for Preventing Post-operative Nausea and Vomiting* is discussed in the section on *Analyses performed across trials (pooled analyses and meta-analyses* in this AusPAR. As noted in the sponsor's Clinical Overview, the Cochrane review authors searched The Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2004), MEDLINE (January 1966 to May 2004), EMBASE (January 1985 to May 2004), CINAHL (1982 to May 2004), AMED (1985 to May 2004), SIGLE (to May 2004), ISI WOS (to May 2004), LILAC (to May 2004) and INGENTA bibliographies. Randomised, controlled trials that compared a drug with placebo or another drug, or compared doses or timing of administration, that reported post-operative nausea or vomiting as an outcome were selected. Each of the authors independently assessed trial quality and extracted outcome data.

This systematic review included randomised clinical trials that compared a drug with placebo or another drug for prevention of PONV, or compared doses or timing of administration and reported PONV as an outcome. Studies of treatment for established PONV were excluded. Study drug could be given pre-operatively, at induction of anaesthesia, intra-operatively or post-operatively (before nausea and vomiting had occurred). It included participants undergoing general anaesthesia, regional anaesthesia

or sedation. Overall the review included 737 studies involving 103,237 people. Sixty different drugs were identified, including cyclizine. Efficacy in prevention of PONV was demonstrated for 8 of these 60 drugs, including cyclizine.

In relationship to cyclizine, the authors of the Cochrane Review assessed the following 10 studies: Ahmed *et al.,* 2000; Chestnutt and Dundee, 1986; Cholwill *et al.,* 1999; Dundee *et al.,* 1975; Grimsehl *et al.,* 2002; Hildyard *et al.,* 2001; Nortcliffe *et al.,* 2003; O'Brien *et al.,* 2003; Walder & Aitkenhead, 1995 and Watts, 1996. In that review, a drug was considered effective if it achieved statistically significant benefits when compared to placebo for all four of the following outcomes: nausea; vomiting; nausea or vomiting; and use of rescue anti-emetic.

The RR for PONV for each of the 8 study drugs that showed a statistically significant difference vs. placebo are shown in Table 28 of this AusPAR. Cyclizine had a RR of 0.65 (95% CI 0.47–0.90) for nausea, 0.57 (95% CI 0.43–0.75) for vomiting and 0.68 (95% CI 0.58–0.80) for nausea or vomiting and 0.27 (95% CI 0.14–0.62) for rescue antiemetic. A comparison of cyclizine and ondansetron was also performed. This showed no statistically significant differences for any of the parameters assessed between the 2 drugs, however there was a trend towards more efficacy with ondansetron for vomiting, nausea or vomiting and use of rescue medication.

The evaluator considered 5 of 12 studies submitted by the sponsor as pivotal and has provided explanations for considering the remaining studies as supportive. The 5 pivotal studies are summarised in Table 10 of this AusPAR. All of these were included in the Cochrane Review. These studies were either double-blind (4 studies) or observer-blind (1 study). In total 487 patients were given either parenteral cyclizine (IV in 3 studies and IM in 2 studies) or ondansetron with or without metaclopramide (3 studies) or placebo (2 studies) at or immediately before induction of anaesthesia. All the pivotal studies were in women undergoing gynaecological surgery.

The study by Cholwill *et al*., 1999 was a double-blind, randomised, placebo and active controlled study comparing ondansetron 4 mg IV with cyclizine 50 mg IV and placebo for the prevention of PONV for 24 h after day-case gynaecological laparoscopy. All patients were ASA I or II and were stratified by history of PONV. The primary outcome measures were the incidence of moderate or severe nausea, vomiting and the number of patients receiving escape antiemetic.

A total of 175 patients were randomised across the 3 treatment groups. Average age in the 3 groups was from 31 to 33 years (range 22 to 50 years). From 19% (placebo group) to 25% (cyclizine group) had histories of PONV. Most patients were undergoing laparoscopic sterilisation. Moderate or severe nausea was reported by 3 (23%) patients given cyclizine, 18 (30%) given ondansetron and by 30 (52%) given placebo. Escape antiemetic was given to 9 (16%) patients given cyclizine, 17 (28%) given ondansetron and 27 (47%) given placebo. These results were statistically significant for comparisons of both cyclizine and ondansetron with placebo. No statistical comparison of cyclizine vs. ondansetron was performed. Vomiting occurred in 13 (23%), 19 (32%) and 24 (41%) patients given cyclizine, ondansetron and placebo respectively. These differences were not statistically significant.

The second pivotal study was reported by Grimsehl *et al*., 2002. This was a randomised, double-blind, active controlled study that compared cyclizine 50 mg IV with ondansetron 4 mg IV at induction. 64 patients were enrolled. PONV was reported in 21 (56%) patients given cyclizine and in 20 (54%) given ondansetron. Severe nausea was reported in 6 (16%) patients in each group and vomiting in 6 (16%) patients given cyclizine and in 4 (11%) given ondansetron. The difference in incidence of PONV between the treatments groups was not statistically significant. This was a small study powered to demonstrate

between treatment differences of 35% or more in the incidence of PONV. No such differences were demonstrated.

The study by Watts (1996) had an initial open sub-study in which 38 patients underwent a procedure without prophylactic antiemetic and data from that sub-study were used to establish an expected rate of PONV in the subsequent randomised, double-blind, comparative study in which patients received IV cyclizine 50 mg, ondansetron 4 mg or metoclopramide 10 mg immediately before induction. All patients received the same anaesthetic protocol. The primary outcome measure in this study was PONV measured as either requiring treatment of nausea or having an emetic episode.

In the sub-study, 18/38 (47%) patients required treatment for PONV. In the main study clinical nausea was reported in 27 (50%) patients given cyclizine, 12 (20%) given ondansetron and 13 (24%) given metoclopramide. Overnight admissions due to severe PONV were reported for 4 patients given cyclizine and 2 given ondansetron. Nausea was also assessed on a 4 point scale from 0 to 3 where 0 = absence of PONV, 1 = mild nausea settling spontaneously, 2 = nausea requiring treatment and 3 = actual emetic episode. Nausea scores were determined in the recovery room at 2 h post- surgery, at discharge, and at 24 h post-surgery. Statistically significant differences in nausea scores favouring both ondansetron and metoclopramide over cyclizine were reported at the 2 h post-surgery and at discharge timepoints.

The study by Chestnutt and Dundee, 1986 was a double-blind, placebo-controlled study to compare efficacy and safety of cyclizine and perphenazine (a typical antiphychotic) given in conjunction with meptazinol (an opioid analgesic). Intramuscular cyclizine 50 mg, perphenazine 2.5 mg or saline was given 1.5 h preoperatively. The primary outcome measure was the incidence of slight or marked nausea and vomiting (alone or with nausea). This was assessed pre and post-operatively and overall. Forty patients were randomised to each group. The overall incidence of either nausea or vomiting was 33/40 (82.5%) for placebo, 22/40 (55%) for cyclizine and 34/40 (85%) for perphenazine.

Cyclizine statistically significantly reduced nausea or vomiting compared with placebo and with perphenazine at the pre-operative and post-operative assessments and overall.

Dundee *et al*., 1975 was the final published study report considered pivotal. This was a double-blind study comparing pre-operative IM cyclizine 50 mg and perphenazine 2.5 mg or 5.0 mg in women undergoing a minor gynaecological operation with a standard anaesthetic including opioids (morphine or pethidine). This study was randomised initially then amended to permit allocation by a clinician other than the investigators to balance the numbers in each group who had or had not had dilatation of the cervix uteri in each group. Initially 100 patients were randomised to each group. The 5 mg perphenazine group was withdrawn during study due to a high incidence of restlessness.

The objective was to assess the incidence of PONV of cyclizine versus perphenazine and placebo. Outcome measures were the incidences of pre and post-operative nausea and/ or vomiting. Results for this study were presented by sub-group receiving pethidine (n=300), morphine 10 mg (n=200) and morphine 15 mg (n=100). Each of the 3 antiemetic groups were thus assessed efficacy in subgroups given for each of the 3 opioids regimens. This had the effect of reducing the power of the study to detect statistically significant differences. Nevertheless it was reported that both cyclizine and 2.5 mg perphenazine were statistically significantly superior to placebo in reducing PONV in patients who received pethidine. Whether this study controlled for multiplicity effects in its statistical analysis is not clear. Overall, the Delegate did not consider this study suitable as a pivotal study due to the lack of information on method and timing of administration of study medications and on statistical methods.

The proposed indication of treatment of PONV caused by narcotic analgesics was investigated in 3 studies discussed in the section on *Efficacy studies – The treatment of nausea and vomiting caused by narcotic analgesics* of this AusPar. The first by Chestnutt and Dundee, 1986 was included in the Cochrane systematic review and is discussed above. That study had many subgroups (3 subgroups in each of the 3 treatment groups) and was a relatively small study. I am not satisfied it was adequate to assess the relative efficacy of cyclizine or perhenazine in preventing or treating PONV due to either opioids or general anaesthetics. The second study investigating treatment of PONV (Dundee *et al*., 1975) was also discussed as a pivotal study for prevention of PONV. Two further studies by Dundee or co-authored by Dundee in the 1960s were submitted to support a specific statement regarding treatment of PONV due to narcotic analgesics. These studies are described in the section on *Efficacy studies – The treatment of nausea and vomiting caused by narcotic analgesics*.

Only one published paper was submitted in support of the proposed indication of *pre-operative use in patients undergoing emergency surgery to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia.* This was a 1977 paper in which lower oesophageal sphincter pressure was measured in 8 healthy volunteers who were quietly resting in the supine position after a 5 h fast. The subjects had not received a general anaesthetic. Lower oesophageal sphincter pressures were measured before and after 25 mg cyclizine IV and a mean increase in pressure was noted.

Safety

Safety data from published studies are usually limited. This is particularly the case for older published studies such as those included in this submission. The clinical evaluator has noted that sedation/drowsiness was the most common adverse drug reactions in clinical trials. Many of the adverse events are consistent with central anticholinergic effects. Most safety information has come from post-market sources as described in the section on *Post marketing experience* of this AusPAR. Cyclizine has been available internationally since the 1960s. Nervous system disorders were the most frequently reported adverse events and included alterations to consciousness, convulsions, dizziness, extrapyramidal effects, and reduced level of consciousness.

Psychiatric reactions including hallucinations and disorientation, and allergic reactions including severe anaphylaxis have also been reported (the sponsor's *Clinical Overview* refers). Local injection site reactions including muscle necrosis were reported with continuing IM use. The clinical evaluator noted that agranulocytosis had been reported as an adverse event. This appears to be based on one post-market report of a woman who developed agranulocytosis 6 weeks after receiving 3 doses of 50 mg cyclizine (the sponsor's *Clinical Overview* refers).

There are considerable data relating to the use of cyclizine in pregnancy however this use is not in the context of single dose use for prevention of PONV. The documentation on the safety of cyclizine use in pregnancy is summarised in Table 46 of this AusPAR.

Cyclizine has potential for abuse and dependency. This is unlikely in the context of single dose use for prevention of PONV however it is clear that cyclizine has caused dependence when given for other indications or when taken without indication. Four cases of abuse of IV cyclizine were reported in patients with cancer. Abuse can be associated with aggression and seizures. Six cases of accidental overdose in children were consistent with anticholinergic syndrome with signs and symptoms including hallucinations, disorientation, tachycardia, flushing, fever, and mydriasis. Seizures have also been reported in the context of cyclizine overdose.

Risk management plan

The RMP evaluator considered the submitted RMP was supportive of the application and recommended that implementation of the RMP and the sponsor's responses to TGA questions (pertaining to the RMP) be imposed as a condition of registration when so qualified. Routine pharmacovigilance activities have been proposed. The sponsor has indicated there is potential for off-label use in palliative care for nausea, possible use in children and use in the management of vestibular disease. The sponsor intends to inform prescribers of the licensed indication for Valoid. Amendments to the draft PI were recommended.

Risk-benefit analysis

Delegate considerations

The quality evaluator considered that approval of this submission could not be recommended until a suitable method for monitoring the finished product had been developed and appropriate stability data using that method was generated. This subsequently occurred and there are no current pharmaceutical chemistry objections to registration.

Data on the pharmacokinetics of cyclizine are extremely limited. There were no data on the pharmacokinetics of cyclizine given in repeat doses, in the 50 mg dose proposed, or for IM administration. It could not be established from the data presented that the pharmacokinetics of cyclizine are linear. As a minimum the sponsor should have provided data to demonstrate the pharmacokinetics of cyclizine given with the regimen and routes of administration proposed for registration.

In overdose cyclizine has similar effects to that of other centrally acting antihistamines. The study on oesophageal sphincter tone appears to be the basis for the statement in the *Pharmacodynamic* section of draft PI that cyclizine increases lower oesophageal sphincter tone and reduces the sensitivity of the labyrinthine apparatus. It may inhibit the part of the midbrain known collectively as the emetic centre. The proposed dose is likely to adversely affect individuals who have heart failure and its use should not be recommended in patients with severe heart failure.

Assessment of efficacy of cyclizine in reducing PONV has relied primarily on older published studies using comparators that in some cases, including in the pivotal studies, are not registered in Australia for the proposed indication. Differences in the incidences of PONV vary with the anaesthetic regimen used, the patient group, surgical procedure and past-history of PONV in the individual patients. The studies presented were mostly small. All these factors contribute to inconsistent efficacy results across studies.

The *Cochrane Review* was helpful in establishing some degree of efficacy of cyclizine in prevention of PONV and assessment of 5 of the 10 studies involving cyclizine in that review are sufficient, in my view to establish that the proposed dose of cyclzine, given either by IV or IM in the peri-operative period reduces the incidence of PONV.

No evidence the cyclizine is an effective treatment for established PONV was included in the submission. There was insufficient evidence that cyclizine has a specific role in treatment of PONV due to narcotic analgesics to permit a specific indication referring to narcotic analgesics. The studies examining this indication were very old and had major limitations, including insufficient information on the method of statistical analysis.

It is clear that cyclizine, given at the proposed dose of 50 mg either IM 1.5 h prior to surgery or IV at induction has some efficacy in reducing PONV. Efficacy appears to vary between studies, as would be anticipated given the other factors that influence PONV.

The proposed indication of *pre-operative use in patients undergoing emergency surgery to reduce the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia* is not supported by adequate evidence. The only study in support of that indication is insufficient because: only 8 subjects were assessed; they had not received a general anaesthetic which would reduce LOS tone; the proposed dose of cyclizine was not given; and the lower oesophageal sphincter pressure that would prevent regurgitation during a general anaesthetic has not been established.

Conclusion and recommendation

The Delegate proposes to approve registration of Valoid containing 50 mg cyclizine lactate in 1 mL injection ampoule for

The prevention of nausea and vomiting in the post-operative period.

The advice of the ACPM is specifically requested on the following:

- Should a statement on the cause of the PONV be included in the indication, for example caused by opioids and by general anaesthetic agents?
- Should a time period for use during the post-operative period should be specified in the indication, if so what should that time period be?
- Should treatment of established PONV be included in the indication given the limited data to support this use?
- Should the route of administration be limited to IV in the absence of pharmacokinetic data on the distribution and pharmacokinetics of cyclizine following IM administration.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit-risk profile for the following indication**:**

For the prevention of post-operative nausea and vomiting.

In making this recommendation, the ACPM agreed with the Delegate that there was insufficient evidence to support the proposed broader indication of:

- reduction of the hazard of regurgitation and aspiration of gastric contents during induction of general anaesthesia.
- post operative nausea and vomiting specifically caused by narcotic analgesics

The ACPM did not support the intramuscular administration route due to inadequate pharmacokinetic data and the absence of safety data for this route.

The ACPM advised that the amendments to the PI and CMI include:

- a statement in the *Clinical Trials section* to reflect that the principal studies were conducted in young female patients only and may include data from older studies that may not align with current anaesthetic regimens and practice.
- Inclusion in all appropriate sections including the *Contraindications* and *Dosage and Administration* sections to strengthen the overall description of the cardiovascular effects and specifically the safety risks for patients with cardiac failure. Highlight that the data supports administration to commence within first 24 hours with duration of therapy limited to 48 hours.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Valoid 50 mg/1 mL cyclizine lactate injection ampoule for IV administration at a dose of 50 mg up to three times daily, indicated for:

the prevention of nausea and vomiting in the post operative period.

Specific conditions of registration applying to these therapeutic goods

1. The implementation in Australia of the cyclizine lactate Risk Management Plan (RMP), included with the sponsor's responses to TGA requests for information in relation to this submission, and any subsequent revisions, as agreed with the TGA and its OPR.
2. The provision of a copy of the proposed additional educational material for healthcare professionals, as described in your responses to TGA requests for information, to the TGA, for information post registration.

VII. References

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Appendix I

PSUR 1st November 2004 to 30th June 2008. AEs by Preferred Term

MedDRA Preferred Term	Total AEs	No. Serious Unlisted AEs	No. Serious Listed AEs	No. Non-serious Unlisted AEs	No. Non-serious Listed AEs
Infections and Infestations					
Nasopharyngitis	**1**	1	0		
Pneumonia	**1**	1	0		
Ear infection	**1**	1	0		
Immune system disorders					
Anaphylactic reaction	**6**	0	6		
Hypersensitivity	**2**	0	2		
Drug hypersensitivity	**1**	0	1		
Metabolism and nutrition disorders					
Tetany	**1**	0	0	1	0
Anorexia	**1**	1	0	0	0
Psychiatric disorders					
Hallucination, visual	**4**	0	4	0	0
Hallucination	**11**	0	11	0	0
Hallucination, mixed	**1**	0	1	0	0
Hallucination, auditory	**1**	0	1	0	0
Abnormal behaviour	**1**	1	0	0	0
Agitation	**4**	4	0	0	0
Anxiety	**2**	2	0	0	0
Bruxism	**1**	1	0	0	0
Confusional state	**15**	0	15	0	0
Depression	**1**	1	0	0	0
Disorientation	**5**	0	5	0	0
Dysphoria	**1**	1	0	0	0
Emotional distress	**1**	1	0	0	0
Fear	**1**	1	0	0	0
Mood altered	**1**	1	0	0	0
Nightmare	**1**	1	0	0	0
Panick attack	**1**	0	0	1	0
Psychiatric disorder	**1**	1	0	0	0
Staring	**1**	1	0	0	0

Nervous system disorders

Extrapyramidal disorder	**5**	0	4	0	1
Dizziness	**27**	0	18	0	9
Akathisia	**1**	1	0	0	0
Amnesia	**2**	2	0	0	0
Aphasia	**2**	0	2	0	0
Areflexia	**2**	2	0	0	0
Bradykinesia	**1**	1	0	0	0
Cerebrovascular accident	**1**	1	0	0	0
Chorea	**1**	0	1	0	0
Cognitive disorder	**1**	1	0	0	0
Convulsion	**2**	0	2	0	0
Depressed level of consciousness	**3**	0	3	0	0
Diplegia	**1**	1	0	0	0
Dysarthria	**11**	0	11	0	0
Dysgeusia	**1**	1	0	0	0
Dyskinesia	**9**	0	8	0	1
Dysphasia	**1**	1	0	0	0
Dysstasia	**1**	1	0	0	0
Dystonia	**11**	0	11	0	0
Grand mal convulsion	**2**	0	2	0	0
Headache	**4**	0	4	0	0
Hypoaesthesia	**6**	0	4	0	2
Hypokinesia	**1**	1	0	0	0
Loss of consciousness	**7**	7	0	0	0
Masked facies	**1**	1	0	0	0
Monoplegia	**1**	1	0	0	0
Movement disorder	**2**	0	2	0	0
Neurological symptom	**1**	1	0	0	0
Nystagmus	**1**	1	0	0	0
Opisthotonuos	**1**	0	1	0	0
Paraesthesia	**18**	0	8	0	10
Paralysis	**4**	4	0	0	0
Paralysis flaccid	**1**	1	0	0	0
Parkinson's disease	**1**	1	0	0	0
Partial seizure	**1**	0	1	0	0
Sensory disturbance	**5**	0	0	5	0
Sensory loss	**1**	1	0	0	0
Somnolence	**7**	0	6	0	1
Speech disorder	**4**	0	4	0	0
Tardive dyskinesia	**1**	1	0	0	0
Tremor	**12**	0	10	0	2
Unresponsive to stimuli	**6**	6	0	0	0

Eye disorders

Diplopia	**2**	2	0	0	0
Eyes rolling	**2**	2	0	0	0
Eyelid oedema	**1**	1	0	0	0
Eyelid ptosis	**1**	1	0	0	0
Eyelid retraction	**1**	1	0	0	0
Gaze palsy	**1**	1	0	0	0
Mydriasis	**1**	1	0	0	0
Oculogyration	**6**	0	5	0	1
Photophobia	**1**	1	0	0	0
Photopsia	**2**	0	0	2	0
Pupils unequal	**1**	1	0	0	0
Vision blurred	**5**	0	3	0	2

Ear and labyrinth disorders

Vertigo	**1**	1	0

Cardiac disorders

Atrial fibrillation	**1**	1	0	0	0
Atrial flutter	**1**	1	0	0	0
Cardiac arrest	**1**	1	0	0	0
Cyanosis	**1**	1	0	0	0
Palpitation	**3**	3	0	0	0
Supraventricular tachycardia	**2**	2	0	0	0
Tachycardia	**21**	0	18	0	2
Ventricular extrasystoles	**1**	1	0	0	0
Ventricular fibrillation	**1**	1	0	0	0

Vascular disorders

Flushing	**4**	3	0	1	0
Hypertension	**13**	0	10	0	3
Hypotension	**9**	6	0	3	0
Pallor	**3**	3	0	0	0
Vein disorder	**1**	0	1	0	0

Respiratory, thoracic and mediastinal disorders

Aspiration	**1**	1	0	0	0
Bronchospasm	**1**	1	0	0	0
Dry throat	**1**	0	1	0	0
Dyspnoea	**13**	9	0	4	0
Pharyngolaryngeal pain	**1**	1	0	0	0
Respiratory disorder	**2**	2	0	0	0
Respiratory failure	**2**	2	0	0	0
Stridor	**1**	1	0	0	0
Throat irritation	**1**	0	1	0	0
Throat tightness	**1**	0	1	0	0
Wheezing	**1**	1	0	0	0

Gastrointestinal disorders

Abdominal distension	**1**	1	0	0	0
Constipation	**1**	0	1	0	0
Diarrhoea	**1**	1	0	0	0
Dry mouth	**10**	0	10	0	0
Dyspepsia	**1**	1	0	0	0
Dysphagia	**4**	4	0	0	0
Flatulence	**1**	1	0	0	0
Gastroesophageal reflux disease	**1**	1	0	0	0
Nausea	**6**	6	0	0	0
Necrotising enterocolitis neonatal	**1**	1	0	0	0
Retching	**1**	1	0	0	0
Swollen tongue	**2**	0	2	0	0
Vomiting	**1**	1	0	0	0
Vomiting projectile	**1**	0	0	1	0

Hepatobiliary disorders

Jaundice cholestatic	**1**	0	1

Skin and subcutaneous tissue disorders

Angioedema	**2**	0	2	0	0
Angioneurotic oedema	**1**	0	1	0	0
Blisters	**4**	2	0	2	0
Cold sweat	**2**	2	0	0	0
Erythema	**7**	0	5	0	2
Hyperhidrosis	**2**	2	0	0	0
Hypoaesthesia, facial	**1**	0	1	0	0
Maculopapular rash	**1**	0	1	0	0
Pruritis	**3**	3	0	0	0
Rash	**5**	0	3	0	2
Rash macular	**2**	0	2	0	0
Scab	**1**	1	0	0	0
Skin burning sensation	**1**	0	1	0	0
Skin discolouration	**1**	1	0	0	0
Skin irritation	**2**	0	0	0	2
Swelling face	**1**	0	1	0	0
Urticaria	**1**	0	1	0	0

Musculoskeletal and connective tissue disorders

Asthenia	**1**	1	0	0	0
Mobility decreased	**1**	1	0	0	0
Muscle disorder	**1**	1	0	0	0
Muscle rigidity	**2**	2	0	0	0
Muscle spasms	**6**	0	3	0	3
Neck pain	**1**	1	0	0	0
Pain in extremity	**1**	1	0	0	0
Sensation of heaviness	**4**	4	0	0	0
Twitching	**1**	0	1	0	0

Renal and urinary disorders

Urinary retention	**1**	0	1

Pregnancy, puerperium and peri natal disorders

Intra-uterine death	**1**	1			
Meconium abnormal	**1**	1			
Normal baby	**1**				1
Premature baby	**2**	2			

Reproductive system and breast disorders

Metrorrhagia	**1**	1	
Vaginal discharge	**1**	1	

General disorders and administration site conditions

Abasia	**1**	1	0	0	0
Adverse drug reaction NOS	**1**	1	0	0	0
Asthenia	**4**	4	0	0	0
Catheter site related reaction	**2**	0	1	0	1
Chest discomfort	**1**	1	0	0	0
Chest pain	**3**	3	0	0	0
Chills	**6**	5	0	1	0
Drug ineffective	**2**	2	0	0	0
Drug interaction	**1**	1	0	0	0
Drug withdrawal syndrome	**1**	1	0	0	0
Fat necrosis	**1**	1	0	0	0
Feeling abnormal	**1**	0	0	1	0
Feeling drunk	**2**	2	0	0	0
Infusion site pain	**1**	0	1	0	0
Infusion site phlebitis	**1**	0	0	0	1
Infusion site erythema	**1**	0	0	0	1
Injection site irritation	**5**	0	3	0	2
Injection site pain	**6**	0	3	0	3
Injection site reaction	**1**	0	1	0	0
Injection site swelling	**1**	0	0	0	1
Irritability	**1**	1	0	0	0
Local swelling	**1**	1	0	0	0
Malaise	**6**	5	0	1	0
Necrosis	**1**	1	0	0	0
Neurological symptom	**1**	1	0	0	0
Oedema peripheral	**2**	2	0	0	0
Pain	**2**	0	0	0	2

Investigations

Alanine aminotransferase increased	**1**	0	1
Blood pressure decreased	**2**	2	0
Blood pressure increased	**3**	0	3
Electrocardiogram PR prolongation	**1**	1	0
Heart rate increased	**4**	0	4
Oxygen saturation decreased	**1**	1	0
Pulse absent	**1**	1	0
Respiratory rate decreased	**1**	1	0
Weight decreased	**1**	1	0

Injury, poisoning and procedural complications

Accidental overdose	**1**	0	0	0	1
Contusion	**1**	1	0	0	
Drug administration error	**1**	0	0	1	
Drug exposure during pregnancy	**10**	0	2	0	8
Drug toxicity	**1**	1	0	0	
Intentional drug misuse	**1**	0	1	0	
Intentional overdose	**1**	**1**	**0**	**0**	**0**

Surgical and medical procedures

Laparotomy	**1**	1	0
Off label use	**1**	1	0

Appendix II

Immune system disorders

MedDRA Preferred Term	Total AEs	Serious Unlisted AEs	Serious Listed AEs	Non-serious Unlisted AEs	Non-serious Listed AEs
Anaphylactic reaction	3	0	3		

Psychiatric disorders

Emotional distress	1	1	0	0	0
Drug craving	1	1	0	0	0
Drug abuse	4	4	0	0	0
Mental agitation	1	1	0	0	0
Drug dependence	1	1	0	0	0
Euphoria	1	0	0	0	1
Confusion	4	4	0	0	0
Agitation	1	1	0	0	0
Disorientation	3	0	1	0	2
Visual Hallucination	2	0	2	0	0

Nervous system disorders

Involuntary muscle movement	2	0	1	0	1
Incoherent	1	1	0	0	0
Slurred speech	3	0	3	0	0
Dystonic reaction	3	0	3	0	0
Unresponsive to stimuli	2	2	0	0	0
Acute dystonia reaction	2	0	2	0	0
Lightheadedness	2	0	2	0	0
Tongue movement disturbance	2	2	0	0	0
Cholinergic reaction	1	1	0	0	0
Dizziness	1	0	1	0	0
Facial droop	1	1	0	0	0
Transient Ischemic reaction	2	2	0	0	0
Weakness left or right side	1	1	0	0	0
Shaking	1	0	1	0	0
Unresponsive to verbal stimuli	1	0	0	0	1
Pins and needles	1	0	0	0	1
Restless legs	2	1	0	1	0
Drowsiness	1	0	1	0	0
Depressed level of consciousness	1	0	1	0	0
Aphasia	1	0	1	0	0
Consciousness decreased	1	0	1	0	0
Hard to awaken	1	1	0	0	0
Tingling skin	1	0	1	0	0
Extrapyramidal disorder	3	0	2	0	1
Grand mal conculsion	1	0	1	0.	0
Syncope	1	1	0	0	0
Tonic Clonic Seizures	2	0	2	0	0
Numbness	1	1	0	0	0
Jerky movements	2	0	1	0	0

Eye disorders

Visual Disturbance	1	0	0	0	1
Blurred vision	1	0	1	0	0

Cardiac disorders

Tachycardia	4	0	1	0	3
Cardiac Arrest	1	1	0	0	0

Vascular disorders

Thoraicabdominal aortic aneurysm	1	1	0
Hypotension	1	0	1
Flushed	1	1	0
Phlebitis	1	0	1

Respiratory, thoracic and mediastinal disorders

Apnoea	1	0	1
Hyperventilation	1	1	0
Throat swell	1	1	0

Gastrointestinal disorders

Lip swelling	1	1	0
Swollen lips	1	1	0
Abdominal pain	1	1	0

Skin and subcutaneous tissue disorders

Itchy	2	2	0
Redness	1	0	1
Widespread rash	1	0	1
Rash Erythematous	1	0	1

Musculoskeletal and connective tissue disorders

Weakness of limbs	1	1	0
Sensation of heaviness	1	1	0
Muscular weakness	1	1	0
Pain in legs	1	1	0

Pregnancy, puerperium and peri natal disorders

Intrauterine death	1	1	0	0	0
Normal baby	1	0	0	0	1

General disorders and administration site conditions

No adverse reaction	1	0	0	1	0
Lack of drug effect	2	0	0	2	0
Administration site reaction	1	0	0	0	1
Tiredness	1	0	0	0	1
Reaction site hypertrophy	1	0	0	1	0
Drug intolerance	1	1	0	0	0
Feeling strange	1	1	0	0	0
Injection site necrosis	1	1	0	0	0
Chest tightness	1	1	0	0	0
Inflamation injection site	2	0	0	0	2
Injection site reaction	1	0	0	0	1
Strength loss of	1	1	0	0	0

Investigations

Heart rate increased	2	0	2	0	0
GGT Increase	1	0	0	0	1
Glasgow coma scale abnormal	1	1	0	0	0
Urine colour abnormal	1	0	0	1	0

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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