



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Ephedrine Hydrochloride

Proprietary Product Name: Ephedrine
Hydrochloride MYX

Sponsor: Mayne Pharma International Pty Ltd

June 2017

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The 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 <<https://www.tga.gov.au>>.

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- An Australian Public Assessment Report (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; it provides 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.

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Common abbreviations

Abbreviation	Meaning
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ASA	American Society of Anaesthetists
ASA I (or II)(or III)	American Society of Anaesthetists physical status classification system
BD	Twice daily
CEP	European Pharmacopeia Certificate of suitability
CHMP	Committee for Medicinal Products for Human Use
EDQM	European Directorate for the Quality of Medicines
FDA	Food and drug administration
HR	Heart rate
IM	Intramuscular
IV	Intravenous
MAOI	Monoamine oxidase inhibitor
MAP	mean arterial pressure
PAR	public assessment records
PARs	Physical activity on prescription schemes
PI	Product information
PSURs	periodic safety update reports
UK	United kingdom
USA	United states of America

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major variation (new strength)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	18 July 2016
<i>Date of entry onto ARTG</i>	21 July 2016
<i>Active ingredient:</i>	Ephedrine Hydrochloride
<i>Product name:</i>	Ephedrine Hydrochloride MYX
<i>Sponsor's name and address:</i>	Mayne Pharma International Pty Ltd PO Box 7000 Salisbury SA 5108
<i>Dose form:</i>	Injection solution
<i>Strength:</i>	25 mg/ 1 mL
<i>Container:</i>	ampoule
<i>Pack size:</i>	5 ampoules
<i>Approved therapeutic use:</i>	<i>Ephedrine Hydrochloride MYX injection is indicated in the treatment of hypotension secondary to spinal anaesthesia.</i>
<i>Route of administration:</i>	Intravenous
<i>Dosage:</i>	Lowest effective dose up to a maximum of 30 mg
<i>ARTG number:</i>	243672

Product background

This AusPAR describes the application by Mayne Pharma International Pty Ltd (the sponsor) to register Ephedrine Hydrochloride MYX injection for the following indication:

Ephedrine hydrochloride is indicated in the treatment of shock unresponsive to fluid replacement. It is also indicated in the treatment of hypotension secondary to spinal anaesthesia. Ephedrine hydrochloride has also been used in the treatment of bronchial asthma and reversible bronchospasm although more selective agents (beta adrenergic agonists) are now available.

This is a submission to register a new formulation (new salt) of ephedrine and a new strength.

Ephedrine sulfate 30mg/1 mL injection is currently on the register (ARTG) for the indication:

Ephedrine sulfate is indicated in the treatment of shock unresponsive to fluid replacement. It is also indicated in the treatment of hypotension secondary to spinal

anaesthesia. Ephedrine Sulfate has also been used in the treatment of bronchial asthma and reversible bronchospasm although more selective agents (beta adrenergic agonists) are now available.

Ephedrine is a substituted amphetamine and structural metamphetamine analogue. It is a sympathomimetic with direct and indirect effects on adrenergic receptors. It acts indirectly by enhancing the release of noradrenaline from storage sites in the sympathetic nerves to the effector organ. It has weak alpha- as well as beta₁ and beta₂-adrenergic activity and has pronounced stimulating effects on the central nervous system (CNS). It has more prolonged although less potent effects than adrenaline. Because of the mixed alpha and beta effects it does not reduce uterine blood flow, unlike pure alfa agonists.

The sponsor has proposed that the product will be a pharmaceutical alternative to ephedrine sulfate which is currently marketed in Australia.

Regulatory status

Ephedrine sulfate is a grandfathered product and has been registered since 1984.

At the time the TGA considered this application for Ephedrine Hydrochloride MYX, a similar application had been approved in the European Union, in Italy (National registration on 8 November 1993) for the treatment of acute bronchospasm, and treatment and prevention for hypotension induced by spinal, epidural or intrathecal anaesthesia. No submissions have been made to the Netherlands, Sweden and United Kingdom, United States of America, Canada, Switzerland, New Zealand or Singapore. This drug product is not subject to any deferrals, withdrawals or rejections in any country.

Product information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Introduction

There are currently two products containing ephedrine on the ARTG. Hospira Ephedrine Sulfate Injection (AUST R. 224845) and DBL Ephedrine Sulfate (AUST R. 16325). These products both contain the ephedrine sulfate salt at a concentration of 30 mg/1 mL.

The concentration of the ephedrine free base in the proposed product and the currently registered products is presented in Table 1.

Table 1: Concentration of ephedrine free base in ephedrine sulfate and ephedrine hydrochloride

Ephedrine products	Ephedrine Sulfate	Ephedrine hydrochloride
Salt concentration	30 mg/mL	25 mg /mL
Molar ratio – salt: free base	1:2	1:1

Ephedrine products	Ephedrine Sulfate	Ephedrine hydrochloride
Free base concentration ¹	$(30/428.54)*2*165.23 = 23.13 \text{ mg/mL}$	$(25/201.69)*1*165.23 = 20.48 \text{ mg/mL}$

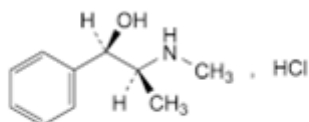
It can be seen that the amounts of ephedrine base in each of the two salts is different and on that basis, the proposed product is considered to be a new strength as it delivers approximately 10% less ephedrine (on a mg basis) per mL of solution compared to the existing (ephedrine sulfate) products. The sponsor states that the difference in potency can be considered to be minor given that the approved ephedrine sulfate and proposed ephedrine hydrochloride MYX PIs recommends that the patient be started with the lowest effective dose and that the drug is titrated until the desired clinical outcome is achieved.

Drug substance (active ingredient)

Ephedrine hydrochloride is white or almost white, crystalline powder or colourless crystals. Ephedrine hydrochloride is freely soluble in water and soluble in ethanol (96 %).

Ephedrine hydrochloride is made by chemical synthesis. The structure contains two chiral centres. The manufacture and quality control according to the applicable British Pharmacopoeia /European Pharmacopoeia (BP/Ph Eur) monograph of the drug substance ephedrine hydrochloride. The EDQM² Certification Database indicates that the European Pharmacopoeia Certificate of suitability (CEP) is valid and up-to-date.

Figure 1: Structure of ephedrine hydrochloride



Ephedrine hydrochloride

Drug product

The product is a colourless solution for injection containing 25 mg/1 mL of ephedrine hydrochloride in water for injections. The formulation does not contain any other excipients.

The product is dissolved in water for injections and is manufactured under nitrogen to minimise oxidation. The solution in bulk is prepared by adding under stirring the required amount of water and the active substance in order to obtain their complete mixing. The product is filtered through a 0.2 micron filter, filled into ampoules and sterilised.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity, extractable volume, pH, particulate contamination, assay impurities, sterility and bacterial endotoxins.

A shelf-life of 3 years when stored at temperatures below 25 °C protected from light is recommended for the proposed drug product.

¹ Molecular weight - Ephedrine sulfate: 428.54; Ephedrine hydrochloride: 201.69; Ephedrine: 165.23

² EDQM = European Directorate for the Quality of Medicines

The sponsor has provided compatibility data to show that their product may be diluted with saline 0.9%.

Biopharmaceutics

Ephedrine hydrochloride is a solution for intravenous injection which is essentially similar to the existing products ephedrine sulfate injection. No biopharmaceutical studies have been conducted. A bio-waver for this type of product is acceptable on the basis that it will be 100% bioavailable. However, the product is a different strength (see introduction, above).

Quality summary and conclusions

The chemistry and quality control aspects were satisfactorily resolved, registration of the product was recommended with respect to quality aspects.

III. Nonclinical findings

Nonclinical summary and conclusions

The only nonclinical issue noted for this application was the inclusion of carcinogenicity and genotoxicity statements in the PI document. This was requested and the sponsor has submitted the relevant statements for TGA assessment.

Presentation of these issues is beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale³

In clinical practice, ephedrine is most commonly used as a pressor agent in obstetric anaesthetics. There are now a number of more selective and efficacious agents for use in asthma. Ephedrine is rarely used in Australia for the management of shock, as there is greater emphasis on initial resuscitation with adequate oxygenation, fluid replacement, and targeted therapy for the cause of shock.

Contents of the clinical dossier

The submission contained the following clinical information:

- Introduction

³ Clarification; The sponsor proposes the use of ephedrine hydrochloride in the treatment of shock unresponsive to volume replacement, hypotension due to spinal anaesthesia, and bronchospasm; all based on an extrapolation of indications for ephedrine sulfate. The stated rationale being that the ephedrine base in each salt is the same active substance and is expected to have the same therapeutic effect.

- Literature references
- Clinical overview, summary of clinical efficacy, summary of clinical safety and literature references.

Paediatric data

The submission did not include paediatric data. However, paediatric use may occur as there are no specific indications or contraindications that would limit its use to adults. The sponsor plans to keep the same dosage and administration information that pertains to children as is in the currently approved DBL Ephedrine Sulfate PI.

Good clinical practice

No sponsor initiated clinical trials were submitted as part of this evaluation.

Pharmacokinetics

Summary of pharmacokinetics

Ephedrine is rapidly absorbed after intramuscular or subcutaneous administration. The onset of action after intravenous administration is immediate; the onset of action after intramuscular administration is 10 to 20 minutes. The duration of pressor and cardiac responses to ephedrine is 1 hour. Small quantities of ephedrine are metabolised in the liver, but the majority of ephedrine is excreted unchanged in the urine. The plasma half-life of ephedrine is 3 to 6 hours. Elimination of ephedrine is increased (and hence half-life decreased) with decreasing pH of the urine. Ephedrine is presumed to cross the placenta and to be excreted in breast milk.

Comment: It is not clear from the submitted data how the pharmacokinetics relates to dose, speed at which the intravenous bolus dose was given, or how the solutions for injection were prepared.

Justification for not submitting biopharmaceutical studies

The sponsor has provided a written statement of justification and included references to journal articles and pharmacopoeia.

The sponsor states that; ephedrine sulfate and ephedrine hydrochloride are not equipotent. However they believe there will be minimal clinical impact of this as the PI *'recommends to start with the lowest effective dose and then give increments until the desired clinical outcome is achieved'*. The sponsor considers that changes in dosing due to the different potency will be well within the therapeutic window and that the risk of dosing error is negligible. A difference of 0.3% sodium chloride between small volume parenteral products is not considered significant.

The sponsor states that ephedrine hydrochloride is interchangeable with other ephedrine salt forms. The sponsor could not find any information in the scientific literature about differences in toxicity of a hydrochloride salt as compared to a sulfate salt. The hydrochloride and sulfate salts have same the solubility in water (Chou 1926),⁴ therefore the sponsor does not expect any pharmacokinetic differences.

⁴ Chou TQ. The preparation and properties of ephedrine and its salts *J. Biol. Chem.* 1926 70: 109-114.

The sponsor states that ephedrine hydrochloride meets the requirements for a parenteral solution biowaiver. The bioequivalence guidelines state that 'bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.'

Comment: The bioequivalence guidelines state that 'different salt, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy'. The sponsor has not provided any evidence to support whether there is or there is not a difference in safety or efficacy between ephedrine hydrochloride or ephedrine sulfate.

The difference between these formulations is not just in the type of salt, but also in the concentration or amount of that salt. Ephedrine sulfate is a heavier molecule, thus the ratio of free base to salt is greater. There is more ephedrine per mL of ephedrine sulfate than there is per mL of ephedrine hydrochloride. In clinical practice, dosing is by milligrams of salt. Ten mg of ephedrine sulfate contains 7.71 mg of free base. Ten mg of ephedrine hydrochloride contains 8.19 mg of free base; this represents 6% more free base and potentially 6% greater potency. The effects of this on efficacy and dosing errors was discussed above and further discussed in below.

It is unclear what the sponsor means by 'therapeutic window'. It is also unclear what the lowest effective dose is.

A biowaiver for parenteral products may be considered if the products have the same amount of active substance, and there is no difference in excipients. Ephedrine sulfate 30 mg/mL and ephedrine hydrochloride 25 mg/mL differ by 11% in the amount of salt per mL, 6% in the amount of free base per milligram of salt, and also in their molecular weight and tonicity. The clinical evaluator was not satisfied that the two different salts are similar enough for a biowaiver to be applied. There needs to be further evidence to support this.

Table 2: Comparison of current and new ephedrine formulations

	Current formulation	Proposed formulation	difference
Company	[information redacted]	[information redacted]	
Ingredients	30 mg Ephedrine sulfate 3 mg sodium chloride In a 1 mL glass ampoule	25 mg ephedrine hydrochloride Water for injection Volume 1 mL	16.7% salt dose per mL
Concentration of free base	23.1 mg	20.5 mg	11.2% base dose

Evaluator's conclusions on pharmacokinetics

The sponsor has submitted information from pharmacology texts in relation to the pharmacological profile of ephedrine. It is reasonable to expect the efficacy and safety of

the ephedrine salt that dissipates from either ephedrine hydrochloride or ephedrine sulfate to have the same pharmacological action.

It is reasonable to assume bioequivalence of two different salts of the same molar concentration if administered intravenously. However, in this case where there is a 6% difference in the amount of base per milligram of salt, a 6% difference in bioavailability and potency would be expected.

It would be expected that the pharmacokinetics of a drug administered intravenously would be affected by the rate at which the dose is administered. There was no information available as to how ephedrine is to be drawn up and administered.⁵

Pharmacodynamics

Studies providing pharmacodynamic data

The sponsor provided information in the form of a clinical and nonclinical overview, and a number of literature references. For further details please see Attachment 2.

Evaluator's conclusions on pharmacodynamics

The mechanism of action of ephedrine has been reasonably well established. However there is limited information on the dose response relationship of either Ephedrine sulfate or ephedrine hydrochloride. It is very difficult to accurately predict the effect of a 6% difference in free base in the proposed formulation without such data. Ephedrine is most commonly used in the context of spinal anaesthesia, particularly in obstetrics. A 6% difference in the free base may have no impact if the dose given is below the therapeutic dose. However, a 6% difference in the amount of active base would have potentially more impact when other drugs that potentiate the effects of ephedrine on α and β receptors for example oxytocin, atropine, cardiac glycosides, hydrocarbon inhalation anaesthetics, antidepressants (monoamine oxidase inhibitors, tricyclic antidepressants noradrenaline reuptake inhibitors), clonidine, and sodium citrate; or if given at a steep part of the slope of a dose response curve.

Efficacy

Studies providing efficacy data

The clinical efficacy for ephedrine hydrochloride is presumed to be the same as that for ephedrine sulfate as both formulations contain the same ephedrine base. The sponsor has submitted a number of journal articles and pharmacology reviews. In addition, the clinical evaluator has performed a literature review and evaluated pharmacopoeia, searched for clinical guidelines, and spoken with anaesthetists in relation to current practice.

Shock unresponsive to fluid replacement

There were no articles submitted to support this indication. The use of ephedrine in this indication is based upon its physiological mechanism of action. In the extract from Martindale's submitted by the sponsor, under the section dosage and administration, it states 'ephedrine is of little value in hypotensive crises produced by shock, circulatory collapse or haemorrhage. It is no longer advocated in orthostatic hypotension.'

⁵ This was resolved in the revised version of the PI

Prevention of hypotension associated with spinal anaesthetic

Literature references have been reviewed for the clinical evaluation for the indication of prevention of hypotension associated with spinal anaesthetic. For details of the evaluation please see Attachment 2.

Evaluator's conclusions on clinical efficacy

Most of the studies do not specify whether ephedrine hydrochloride or sulfate is used, nor do they specify if the dose is for the free base or salt.

All of the studies were examining using ephedrine for the prophylaxis of hypotension with spinal anaesthesia. There was a wide range in reported doses and route of ephedrine used for prophylaxis. The larger doses had greater efficacy. Efficacy varied between studies, however there were a number of confounding factors that had the potential to affect the efficacy including other drugs being administered, whether a fluid bolus was given prior to the spinal needle, the level of the spinal block, the timing of the injection, the route and dose of ephedrine used, and the definition of hypotension. All of the studies reported using rescue IV ephedrine at a dose of around 7 to 10 mg for hypotension, which is lower than recommended in the PI.⁶

The clinical evaluator is satisfied that ephedrine is efficacious for the prophylaxis and management of hypotension in the context of spinal anaesthesia. However the most efficacious dose for prophylaxis and rescue treatment remains uncertain based on the ranges used in the published studies. In particular, the rescue dose used in the clinical studies appears to be much lower than described in the PI.⁶

Bronchial asthma and reversible bronchospasm

The sponsor's literature review included studies using oral rather than parenteral ephedrine. There is insufficient evidence to support the use of ephedrine for this indication.

In the excerpt from Martindale's⁷ included in the dossier, under usage and administration, it states 'ephedrine salts have been used as bronchodilators, but the more beta 2 selective sympathomimetics such as salbutamol are now preferred'.

The sponsor will be asked to submit evidence in support of the use of ephedrine hydrochloride for asthma and reversible bronchospasm, in comparison with both placebo and current standard therapy.

Safety

Studies providing safety data

The sponsor submitted a number of journal articles that documented safety profile of adrenaline. Many of these related to effects after oral administration.

Exert from Martindale Error! Bookmark not defined.

Ephedrine has both alpha and beta agonist effects and its commonest adverse effects are tachycardia, anxiety, restlessness and insomnia. Tremor, dry mouth, impaired circulation to the extremities, hypertension and cardiac arrhythmias may also occur. Ephedrine may be used in labour to maintain blood pressure during spinal anaesthesia but may cause

⁶ Clarification: in the original Ephedrine Hydrochloride MYX PI draft and approved DBL Ephedrine Sulfate PI

⁷ Martindale: The Complete Drug Reference; drug monographs: Ephedrine

fetal tachycardia. Paranoid psychosis, delusions, and hallucinations may also follow ephedrine overdose. Prolonged usage has no cumulative effect, but tolerance with dependence has been reported.

Post-marketing data

The sponsor did not submit any post market data within the original dossier to support the use of ephedrine hydrochloride as a 25 mg/ 1mL strength vial.

The only post market safety data that the Signal Investigation Unit of the Pharmacovigilance and Special Product Access Branch of the TGA were aware of related to the use of ephedrine and pseudoephedrine in complementary medicines.

Evaluator's conclusions on safety

There was very little evidence on which to base an assessment on safety. The risks of ephedrine need to be balanced against the risks of untreated hypotension for which the ephedrine is being given.

The sponsor has submitted journal articles illustrating drug interactions and rare complications of ephedrine such as myocardial infarction and cerebral vasculitis. The PI contains a statement about the use of ephedrine with monoamine oxidase inhibitor (MAOI), and the risk of myocardial ischemia and cerebral vasculitis.

Ephedrine has pregnancy category A⁸ in Australia. The results of the study by Ngan kee⁹ on the trans placental passage of ephedrine and effects on the cord blood pH are notable; however there is no corresponding clinical evidence to document its effect on the neonate. Other studies have not demonstrated significant effects on neonatal outcomes. The clinical evaluator would suggest an extra statement in the pregnancy section to describe this finding, however there is insufficient evidence to justify a change in pregnancy category. Other safety questions posed by this submission include:

Safety of ephedrine hydrochloride versus Ephedrine sulfate as the active ingredient

It would be assumed that both salts have the same safety profile.

Safety of the dose formulation

In clinical practice, ephedrine is dosed based on the salt. Thus, the proposed formulation contains 6% more free base than the currently marketed Ephedrine sulfate. Although such a small difference is unlikely to have a clinically significant effect, there is no evidence to base this assessment on. As ephedrine is used to treat an abnormal and potentially dangerous physiological state, it is preferable to use 6% more rather than 6% less of the active substance. The physiological effects of ephedrine are relatively immediate and short acting. Doses can be repeated every 5 to 10 minutes if a single dose is not efficacious, however this is not ideal due to the potential for tachyphylaxis with repeated dosing.

Safety in the proposed doses

There was a large dose range proposed.¹⁰ The level of evidence to support these doses is low.

⁸ Category A: *Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.*

⁹ Ngan Kee WD, et al. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2009; 111: 506-512.

¹⁰ Clarification: based upon the DBL Ephedrine Sulfate PI instructions.

Safety in the proposed indication

Ephedrine appears to be relatively safe for the prevention and treatment of hypotension in the context of spinal anaesthesia. There is insufficient data to assess its safety when used for asthma and shock.

The most common adverse effects from the mechanism of action of the drug (rebound hypertension or tachycardia) are transient and dose dependent.

First round benefit-risk assessment**First round assessment of pharmaceutical equivalence and benefits**

For this application the clinical evaluator will consider if there is sufficient evidence to support the sponsor's claim that ephedrine hydrochloride is a pharmaceutical alternative to ephedrine sulfate, and the benefits of ephedrine for the proposed indications.

The two ephedrine salts would be considered as pharmaceutical alternatives under the committee for medicinal products for human use (CHMP) guideline definition as they are different salts of an active moiety which differ in dose form. In an intravenous form, it would be expected they are bioequivalent in the same molar dose; however there is a 6 percent difference in the amount of free base if dosed according to milligram of salt (as is done in clinical practice). The clinical impact of this is unknown as there is no information provided about the dose response relationship of ephedrine hydrochloride. A 6% difference is unlikely to be clinically significant at a low dose of ephedrine or when administered to otherwise healthy individuals on no other medications, but may be significantly different to an older individual with significant cardiovascular or cerebrovascular disease who is on other medications which would prolong or potentiate the effects. Furthermore the effect of a 6% increase in free base will depend upon where this dose lies on the dose-response curve, and this information is not available. The sponsor has not submitted sufficient information about the pharmacokinetics or pharmacodynamics of ephedrine at different doses and administered via different routes (intravenous (IV) or intramuscular (IM)) to provide an evidence based decision.

The sponsor proposes the use of ephedrine hydrochloride in the treatment of shock unresponsive to volume replacement, hypotension due to spinal anaesthesia, and bronchospasm; all based on an extrapolation of indications for ephedrine sulfate. The stated rationale being that the ephedrine base in each salt is the same active substance and is expected to have the same therapeutic effect.

Ephedrine is widely used in anaesthesia, particularly obstetric anaesthesia. The sponsor has submitted a number of journal articles to support the use of ephedrine in hypotension after spinal anaesthesia. In relation to the route of administration, there is reasonable evidence for the efficacy of the intravenous route, less robust evidence for the intramuscular route and no evidence for the subcutaneous route. The sponsor has not justified the proposed doses.

In relation to the proposed indication of hypotension, the sponsor has not submitted sufficient evidence to determine if ephedrine hydrochloride is an appropriate pharmaceutical alternative to Ephedrine sulfate, is efficacious for this indication, nor the most appropriate dose.

In relation to the proposed indication of asthma and reversible bronchospasm, the sponsor has not submitted sufficient evidence to determine if ephedrine hydrochloride is an appropriate pharmaceutical alternative to Ephedrine sulfate, is efficacious for this indication, nor the most appropriate dose.

First round assessment of risks

There are risks in accepting ephedrine hydrochloride as a pharmaceutical alternative to ephedrine sulfate for the proposed indications. These include

1. Unknown pharmacokinetics and pharmacodynamics of the proposed doses and routes.
2. Assumptions that a 6% difference in molar concentration will equate with a 6% difference in efficacy and safety outcomes without sufficient information about the pharmacokinetics, pharmacodynamics, efficacy or safety.
3. The use of information from product information for ephedrine sulfate which has been outdated by new research and changes in clinical practice.
4. Dosing errors due to changes in the strength of the ephedrine solution.
5. Insufficient information about how to prepare ephedrine for administration, including what diluents to use and the rate at which it should be administered (as this would have considerable impact on the pharmacokinetics and dynamics and therefore efficacy and safety).

The main risks associated with the use of ephedrine sulfate are rebound hypertension and tachycardia, particularly with higher doses or higher infusion rates. It could be assumed that the proposed risks of ephedrine hydrochloride are the same.

First round assessment of benefit-risk balance

At this stage, the benefit risk balance of ephedrine hydrochloride given intravenously for hypotension in the context of spinal anaesthesia is favourable if questions about dosing are addressed and changes to the PI are made. The benefits of the intramuscular and subcutaneous routes have not been demonstrated and therefore the risk-benefit balance is unfavourable for these routes.

The risk-benefit balance for the use of ephedrine for shock unresponsive to fluid replacement and asthma and reversible bronchospasm is unfavourable due to the lack of current evidence to support its use.

First round recommendation regarding authorisation

Under the section 16 of Therapeutic Goods Act 1989 (The Act), therapeutic goods that are of different formulation or dosage form are to be taken as a separate and distinct good, and therefore need to be evaluated under section 25 of The Act.

At this stage, the clinical evaluator would consider authorising the use of ephedrine hydrochloride as a pharmaceutical alternative to ephedrine sulfate, given intravenously, for use in hypotension secondary to spinal anaesthesia, provided the sponsor is able to address the questions in relation to the pharmacokinetics, pharmacodynamics, dosage, safety, efficacy, changes to the product information and development of a risk management plan.

At this stage, there is insufficient data to support the use of an intramuscular or subcutaneous dose used for hypotension in the context of spinal anaesthesia. There is insufficient data to support the use of ephedrine hydrochloride for indications of shock and asthma.

Clinical questions and second round evaluation of clinical data submitted in response to questions.

Please see Attachment 2 for the presentation of the clinical questions and the second round evaluation of clinical data submitted in response to the questions.

Second round benefit-risk assessment

Second round assessment of benefits

The sponsor has included further justification for the use of ephedrine in spinal and other anaesthesia. In addition, further chemistry, pharmacokinetic, pharmacodynamic and clinical data was submitted in relation to the concerns about the 11% change in potency due to different strength.

The evaluator agrees that for a drug such as ephedrine which is used to treat a medical emergency, a market alternative is an advantage.

Second round assessment of risks

The post market data submitted indicated that the use of ephedrine in Italy was not associated with any reported adverse events. The safety profile of ephedrine is well known, and largely due to its pharmacodynamic effect. It is likely to be used only by anaesthetists in a controlled setting, thus adverse events will be closely monitored and treated.

There appears to be little evidence of a clinical risk for the small difference in the amount of free base or salt in the ephedrine hydrochloride versus ephedrine sulphate. The evaluator will defer any comments in relation to how these risks will be mitigated, assuming that this will be assessed by the pharmacovigilance team and the Delegate. Appropriate labelling and education would be important.

Second round assessment of benefit-risk balance

Having revised the indications and PI, the risk benefit balance for the use of ephedrine hydrochloride for the treatment of hypotension due to spinal anaesthesia is favourable.

Second round recommendation regarding authorisation

The clinical evaluator recommends approval of the registration of ephedrine hydrochloride for the indication of 'treatment of hypotension secondary to spinal anaesthesia' and other changes to the PI.

V. Pharmacovigilance findings

The risk management plan (RMP) for this application was requested and subsequently prepared during the evaluation process. The evaluation of the RMP was not available at the time the submission was presented to the advisory committee for prescription medicines (ACPM) for advice¹¹. All issues relating to the RMP were resolved prior to registration.

¹¹ Clarification: the RMP was not available at the time of submission but was provided during the evaluation of the submission.

VI. Overall conclusion and risk/benefit assessment

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

Background

Ephedrine is an alkaloid of Ephedra type plants that are native to south western North America, Europe, North Africa, south western and central Asia and the Western seaboard of South America. It was first isolated in 1885, is on the WHO Model List of Essential Medicines, but is also listed as a table I precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

Ephedrine is a substituted amphetamine and structural metamphetamine analogue with two chiral centres and can exist as 4 stereoisomers, of which one is ephedrine and another is pseudoephedrine. It is a sympathomimetic with direct and indirect effects on adrenergic receptors. It acts indirectly by enhancing the release of noradrenaline from storage sites in the sympathetic nerves to the effector organ. It has weak alpha- as well as beta1 and beta2-adrenergic activity and has pronounced stimulating effects on the CNS. It has more prolonged although less potent effects than adrenaline. Because of the mixed alpha and beta effects it does not reduce uterine blood flow, unlike pure alpha agonists.

It stimulates heart rate (beta adrenergic effects) and constricts peripheral vessels variably increasing peripheral resistance. It has effects on smooth muscle, including the bladder (alpha adrenergic effects) and bronchial smooth muscle (beta effects) and has a stimulant effect on the respiratory centre. Tachyphylaxis to cardiac and pressor effects can develop after some use due to depletion of noradrenaline in the presynaptic terminal.

There are two registered products in Australia that contain ephedrine: Hospira Ephedrine Sulfate Injection (AUST R 224845) and DBL Ephedrine Sulfate (AUST R 16325). Both these products contain the ephedrine sulfate salt at a concentration of 30 mg /mL.

Ephedrine hydrochloride solution for injection is approved for use in New Zealand (30 mg/mL)¹² and in the United Kingdom (30 mg/mL or 3 mg/mL pre-filled syringe).¹³

Ephedrine sulfate solution for injection is available in the US but has not been evaluated or approved by the FDA (grandfathered product), and does not have a FDA approved label.

The ACPM has not previously considered a submission for ephedrine hydrochloride.

Excerpts from guidance documents of relevance to this submission

Section 15.3 of Guidance 15 of the ARGPM¹⁴ states that biopharmaceutic data or a justification for not providing this data are not required for:

- 'Simple aqueous solutions for intravenous injection or infusion. Simple solutions do not include complex solutions such as emulsions, micellar or liposomal solutions.
- Other parenteral routes, for example intramuscular or subcutaneous, provided that the test product is of the same type of solution (aqueous or oily) and contains the same concentration of the same active substance and the same excipients in similar amounts as the reference product.'

¹² Approval in New Zealand is for in the treatment of shock unresponsive to fluid replacement. It is also indicated in the treatment of hypotension secondary to spinal anaesthesia. Ephedrine Hydrochloride Injection has also been used in the treatment of bronchial asthma and reversible bronchospasm although more selective agents (beta-adrenergic agonists) are now available.

¹³ Approval in the United Kingdom is for the treatment of hypotension from spinal or epidural anaesthesia.

¹⁴ Australian Regulatory Guidelines for Prescription Medicines

Appendix II of the EU Guideline¹⁵ states:

Parenteral solutions

Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the drug substance (for example complex formation), or otherwise affect the disposition of the drug substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

In the case of other parenteral routes, for example intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required. Moreover, a bioequivalence study is not required for an aqueous parenteral solution with comparable excipients in similar amounts, if it can be demonstrated that the excipients have no impact on the viscosity.

Quality

The quality evaluator had no objections to the approval of the submission from a quality perspective. The evaluator noted the following characteristics of the product:

- Ephedrine is a white odourless powdered or crystalline substance with a molar mass of 165.23 g/mol made by chemical synthesis. The structure contains two chiral centres. Racemisation does not occur with this product.
- It is freely soluble in water and soluble in 96% ethanol.
- The final product is a colourless solution for injection containing 25 mg/1 mL of ephedrine hydrochloride in water housed in Glass Type I coloured ampoule. The formulation does not contain any other excipients. The solution is compatible with 0.9% NaCl.
- The finished product is appropriately controlled using the finished product specifications that include acceptable tests and limits for appearance, identity, extractable volume, pH, particulate contamination, assay impurities, sterility and bacterial endotoxins.
- A shelf-life of 3 years when stored at temperatures below 25 °C protected from light in is recommended.

The evaluator noted that no biopharmaceutical studies have been conducted to establish the equivalence of ephedrine hydrochloride with the registered ephedrine sulfate products, but has accepted a bio-waiver for this product on the basis that it will be 100% bioavailable and has the same active substance. However, the evaluator noted differences in the amount of free base (free ephedrine) between the registered product and proposed ephedrine hydrochloride product, taking into account the different strengths of the two products in addition to the different salts. The evaluator calculated the differences as shown in Table 1 above.

The proposed product is considered to be a new strength as it delivers approximately 11.2% less ephedrine (on a mg basis) per mL of solution compared to the existing

¹⁵ CPMP/EWP/QWP/1401/98 Rev. 1 EU Guideline on the Investigation of Bioequivalence

(ephedrine sulfate) products. The sponsor states that the difference in potency can be considered to be minor given that the PI recommends that the patient be started with the lowest effective dose and that the drug is titrated until the desired clinical outcome is achieved.

Nonclinical

No nonclinical data were submitted for evaluation; however the nonclinical aspects of the PI were reviewed by the nonclinical evaluator. An effect on fertility statement has been added to the PI, and all other nonclinical information in the PI was considered overall acceptable.

Clinical

The clinical aspects of the submission included a clinical overview and literature references and a document entitled 'introduction' and literature references. Additional discussion with reference material was provided in response to questions.

In response to the first round clinical evaluation report the sponsor withdrew its request for the indications for bronchospasm and shock and withdrew its application for intramuscular and subcutaneous use. The sponsor also changed the dosage and administration section of the PI to include dilution instructions, replace the maximum dose of 150 mg in 24 hours with 30 mg, and has made changes to the overdose section, to remove the specific treatment advice.

In the second round evaluation report the clinical evaluator recommended approval of Ephedrine Hydrochloride MYX for the indication '*Treatment of hypotension secondary to spinal anaesthesia*'.

Pharmacology

Based on the information provided the evaluator summarised the pharmacology of ephedrine as follows:

- The onset of action is immediate with intravenous administration and 10 to 20 minutes for intramuscular administration
- The duration of the pressor action is about 1 hours
- There is a small amount of ephedrine metabolised in the liver but the majority is excreted in the urine
- The plasma half-life is 3 to 6 hours
- Elimination is influenced by urinary pH.

In addition to the pharmacodynamics summary in the background section of this overview (above), the following was discussed:

- The relative potency of ephedrine for β receptors is $\beta 1 > \beta 2 \gg \beta 3$, suggesting that at clinically relevant plasma concentrations, the cardiovascular effects ($\beta 1$ and $\beta 2$) predominate over the lipid mobilisation and thermogenic effects.
- Publications demonstrated a linear relationship between ephedrine concentration and heart rate and a positive hysteresis in the plasma concentration systolic blood pressure curve with repeated dosing (best described as a tolerance model) with orally administered ephedrine in healthy volunteers.

- A study of 60 women scheduled for mastectomy given either nitroglycerine (vasodilator) or trimethaphan (ganglion blocker) to produce a mean arterial pressure (MAP) of 55 to 60 mmHg after the induction of anaesthesia (propofol/vecuronium/2% sevoflurane with 33% oxygen) showed 50% more ephedrine was required to overcome the hypotensive effects of the vasodilator than was required for the ganglion blocker.
- Ephedrine is presumed to cross the placenta and to be excreted in breast milk.
- No bioequivalence studies were conducted in support of the application. A justification was provided on the basis that ephedrine hydrochloride met the requirements of a parenteral solution biowaiver, in that it contains the same active substance as the reference ephedrine sulfate, and it is a simple aqueous solution. The sponsor could not identify specific literature that addressed any differences in toxicity between the hydrochloride and sulfate ephedrine salts.
- The difference in free base between the two salts has been noted and quantified by the quality evaluation (Table 1 above). A 6.3% increase in the amount of free ephedrine base for the hydrochloride compared to the sulfate salt is noted for equal weights of the two salts. The strengths of the two products are however different, and the combination of the increased free ephedrine but a 25 mg strength rather than 30 mg strength results in 11.2% less free base per mL of the proposed ephedrine hydrochloride salt compared to the approved ephedrine sulphate product.

Efficacy

The sponsor did not present a literature based submission to support its application but did provide a clinical overview, and a brief introductory/summary statement in the clinical sections of the dossier. A number of papers were referenced in the overview documents. From those references and a brief review of the literature the evaluator has summarised clinical information considered relevant.

The clinical evaluator considered the sponsor had provided insufficient evidence to support the use of ephedrine hydrochloride for bronchial asthma and bronchospasm, and for shock unresponsive to fluid replacement. The sponsor has withdrawn its request for these indications.

The majority of the journal articles among the references address the efficacy of ephedrine when used in the context of anaesthesia, and in particular, with neuroaxial anaesthesia. In most of the papers the ephedrine salt used is not specified. No head to head comparison of the efficacy of the two ephedrine salts was provided.¹⁶

Ephedrine as preventative treatment

Kol et al 2009¹⁷

This randomised controlled trial conducted in 42 women given either a crystalloid fluid load prophylactic dose of 0.5 mg/kg IV ephedrine or fluid alone at the time of a spinal anaesthetic for caesarean section delivery compared. Heart rate was higher in the ephedrine group, and fewer women developed hypotension (38.1% versus 85.7%) or nausea and vomiting (19% versus 57%). Rescue ephedrine given in 5 mg IV bolus doses to maintain the systolic arterial pressure at more than 80% of the baseline. The time to rescue was 14.9 versus 7.9 minutes and the total dose required was 4.3 ± 5.9 mg and 18.3 ± 12.7 mg in the ephedrine and control groups, respectively. There was no significant difference in neonatal outcomes.

¹⁶ Clarification: The sponsor could not find published evidence of comparison of the two ephedrine salts.

¹⁷ Kol IO et al The effects of intravenous ephedrine during spinal anaesthesia for caesarean delivery: a randomized controlled trial. *J Korean Med Sci.* 2009; 24: 883-888.

*Simon et al 2001*¹⁸

described a study of 108 ASA I and II¹⁹ women given 10mg, 15 mg or 20 mg IV ephedrine 2 minutes after administration of spinal anaesthesia for caesarean section. Hypotension was treated with fluid bolus and 5mg IV ephedrine. A higher proportion of women were hypotensive in the 10 mg group than the other two groups, and the 10 mg also group required more additional ephedrine.

*Iqbal et al 2010*²⁰

In a similar study Iqbal et al 2010 demonstrated in a study of 90 ASA I and II women given 10mg, 15 mg or 20 mg IV ephedrine after receiving spinal anaesthesia for caesarean section, that a 10 mg prophylactic dose did not prevent hypotension in 53.3% of women (compared to hypotension in 13.3% and 3.3% of the 15 mg and 20 mg IV induction groups).

*A Cochrane review of 75 trials*²¹

A Cochrane review of 75 trials (4624 patients) of therapies to prevent hypotension in spinal anaesthesia for caesarean section ephedrine was more effective than crystalloid fluid boluses.

The evaluator also identified Ngan kee et al 2000⁹ who conducted a study of 80 Asian ASA I and II women undergoing elective caesarean section for singleton pregnancies given IV ephedrine 10 mg, 20 mg, or 30 mg, or saline after spinal anaesthesia. The 30 mg IV group had greater heart rate (HR) but less nausea, but 45% had reactive hypertension (> 20% above baseline). Foetal outcomes were the same in both groups.

The sponsor also summarised evidence to support use in the elderly including a study investigating prophylactic use of 12 mg ephedrine or 0.6 mg atropine in patients undergoing spinal anaesthesia for transurethral resection.

Ephedrine in the treatment of hypotension secondary to spinal anaesthesia

*El Safei et al 2015*²²

Described a randomised, double-blind, controlled study of 100 patients ASA II or III aged 40 to 60 years with coronary artery disease given spinal anaesthesia for knee arthroscopy. Baseline concomitant medications were not reported in the publication. Patients were given either a 5 mg IV dose of ephedrine or 5 µg of noradrenaline after the onset of hypotension. The noradrenaline dose was more effective and resulted in less tachycardia. This is likely to be of importance in patients with coronary artery disease. It is noted that the sponsor proposes to add cardiovascular disease as a contraindication to the use of ephedrine.

Additional support from public assessment records

The sponsor provided the public assessment records (PAR) for the ephedrine hydrochloride product in Sweden, Germany and the UK. In each a very brief summary of the clinical evidence submitted that supported registration in each of the countries.

¹⁸ Simon L, et al Dose of prophylactic intravenous ephedrine during spinal anaesthesia for caesarean section. *J Clin Anesth.* 2001; 13: 366-369.

¹⁹ American Society of Anaesthetists physical status classification system. I = healthy person, II = mild systemic disease.

²⁰ Iqbal M.S. et al. Optimal dose of prophylactic intravenous ephedrine for spinal-induced hypotension during caesarean section. *Anaesthesia, Pain and Intensive Care.* 2010; 14: 71-75

²¹ Cyna AM, et al Techniques for preventing hypotension during spinal anaesthesia for caesarean section (Review) 2006 published in The Cochrane Library 2006, Issue 4

²² El Shafei MM et al Norepinephrine versus ephedrine for the prevention of spinal anaesthesia-induced hypotension in coronary artery disease patients undergoing knee arthroscopy *Ain-Shams Journal of Anesthesiology* 2015; 8: 424-428.

In the Swedish PAR provided by the sponsor, the authors refer to the British National Formulary as a source of data in children, in addition to a paper by Taguchi et al (1996)²³. This study examined the effects of intravenous ephedrine (0.1 mg/kg or 0.2 mg/kg) in 104 infants and children (aged 0.1 to 15 years, weight range from 3.8 kg to 68 kg), anaesthetised with 1.0 MAC halothane and nitrous oxide, however, ephedrine is currently contraindicated with halothane anaesthesia.

Safety

The safety information was in the form of a summary of the known safety issues from a pharmacology text and several journal articles.

According to Martindale⁷, the commonest adverse effects were tachycardia, anxiety, restlessness, insomnia. Other effects may include tremor, dry mouth, impaired circulation to the extremities, hypertension and cardiac arrhythmias. Fetal tachycardia was also noted. Overdosage was noted to cause paranoid psychosis, delusions and hallucinations. Prolonged usage has no cumulative effect but tolerance with dependence has been reported.

Co-administration of moclobemide 300 mg twice daily (BD) and ephedrine (two doses of 50 mg 4 hours apart) to 12 healthy adults increased the incidence of headache and palpitations and potentiated the effect of ephedrine on systolic and diastolic blood pressure (potentiation factors 3.2 and 3.8), and reduced heart rate by a factor of 0.6.

A 31 year old woman with no risk factors for cardiac disease had a documented myocardial infarction though due to ephedrine induced vasospasm during an elective gynaecological procedure after receiving 5 mg IV ephedrine for hypotension and bradycardia that was followed by rebound hypertension, tachycardia and chest tightness.

A 44 year old woman with a history of migraine, mitral valve prolapse and atrial tachycardia, for which she took propranolol, developed a deep right frontal lobe haemorrhagic infarction and angiographic features typical of vasculitis after an unspecified dose of ephedrine and rebound hypertension lasting 3 minutes.

A randomised trial of the placental transfer and fetal metabolic effects of phenylephrine (100 µg/mL) and ephedrine (8 mg/mL) titrated to maintain baseline blood pressure in 104 women having an elective caesarean section. The ephedrine group has lower umbilical arterial and venous pH and greater base deficit, and markedly larger lactate, glucose, epinephrine and norepinephrine concentrations than those that received phenylephrine. Maternal epinephrine and norepinephrine concentrations were also greater. The authors attributed the difference to the transfer of ephedrine across the placenta and stimulation of metabolic processes in the fetus, with a possible contribution from higher levels of maternal hormones.

The proposed product has been supplied in Italy since 1993. There were no adverse events reported in the periodic safety update reports (PSURs) from the period December 1998 to April 2011.

The sponsor reviewed and substantially revised the overdose information in the currently registered DBL Ephedrine Sulfate PI based to expert advice sourced by the sponsor on clinical aspects of the submission as a whole.

²³ Taguchi N et al. Hemodynamic Effects of Intravenous Ephedrine in Infants and Children Anesthetized with Halothane and Nitrous Oxide *Anesth Analg* 1996; 82: 568-573.

Risk management plan

At the time the Delegate's overview was written the RMP was under review by the Pharmacovigilance and Special Access Branch of the TGA.

Risk-benefit analysis

This product is a new (hydrochloride) salt of ephedrine, with a different strength (25 mg/mL) than that currently approved in Australia. Weight for weight the hydrochloride salt has 6.3% greater free ephedrine than the sulfate. In the new strength of 25 mg/mL there is a net 11% reduction in free ephedrine/mL compared to the reference product. The submission to register this product is considered a major variation to the current register entry because it is a new formulation and a new strength.

Although a simple aqueous solution containing the same active ingredient as the reference product the hydrochloride salt does not contain the same amount of active ingredient, so the safety and efficacy of the hydrochloride salt requires evidence in its support.

Efficacy

A literature based submission was not provided in support of the product however a review by the sponsor of the literature and other relevant information was provided. Literature references, although not specifically set forth for evaluation, were provided and have been considered. The sponsor has provided physical activity on prescription schemes (PARs) from Europe that summarise the evidence considered when ephedrine hydrochloride products were approved in their respective countries.

The sponsor's evidence is only in support of the use of ephedrine in the context of hypotension induced by spinal anaesthesia. The bulk of the evidence supports preventative use, prior to the onset of hypotension, which is just outside the requested indication. Many of the papers however also describe supplementary incremental dosing with ephedrine if an initial prophylactic dose was inadequate.

The patient groups investigated in the studies presented are predominantly women undergoing caesarean section for delivery. The evidence of the use of ephedrine in spinal anaesthesia in other patient groups is limited and no evidence was provided to support the use of ephedrine in children.

Doses vary; the papers describe incremental boluses in the order of 5 mg to treat the hypotension once established, whereas the product monographs and PARs describe incremental doses in multiples of 3 mg. It is noted that many of the products are a 30 mg/mL strength making multiples of 3 mg easy to administer. The sponsor has amended the dosage and administration section of the draft PI to include dosing in multiples of 3 mg.²⁴

In addition to the lack of evidence to support this change from the dosing instructions of the reference product the sponsor has not provided dilution instructions to easily enable the prescriber to dilute the 25mg/mL strength to a 3 mg/mL solution. Where such calculations are involved there is increased risk of medication error. The sponsor has stated it believes there will be limited clinical impact if its product is handled in the same way as the reference product in current anaesthetic practice (with a resultant 11.2%

²⁴ Clarification; the dosing statement in the approved PI is "Dilute 1 mL of Ephedrine Hydrochloride MYX Injection to 10 mL with saline 0.9% to produce a 2.5 mg/mL solution. This solution should be given as a slow intravenous injection of 2.5 to 5 mg (maximum 10 mg), repeated as needed every 3 to 4 min to a maximum of 30 mg."

reduction in free ephedrine compared to the registered product) because the dosing in the PI clearly advises the use of small incremental doses often.

Ngan kee et al 2000⁹ described a study of 80 Asian ASA I and II women undergoing elective Caesarean Section for singleton pregnancies given IV ephedrine 10 mg, 20 mg, or 30 mg, or saline after spinal anaesthesia. The 30 mg IV group had greater HR but less nausea, but 45% had reactive hypertension (> 20% above baseline). Fetal outcomes were the same in both groups.

Safety and RMP

While the sponsor has relied on the previously established safety information for ephedrine, some supplementary evidence of the safety of ephedrine has been provided. The sponsor has provided additional information on a drug interaction with moclobemide, and one case report each of myocardial infarction and cerebral vasculitis with haemorrhage.

When used in obstetrics, fetal safety is of importance. The sponsor has provided evidence of increased catecholamines and metabolic effects in the fetus including acidemia when the mother is given ephedrine. There is no evidence to suggest these differences were linked to adverse fetal outcomes. The clinical evaluator has made recommendations for the safety specifications of the RMP in this regard.

The labels on the carton and the ampoule clearly denote the strength to be 25 mg in 1 mL. It should be very clear to the user this is a different strength as well as a different ephedrine salt from the currently approved product. The sponsor also proposes an education campaign in the form of the distribution of posters.

The clinical importance of the difference in free ephedrine between ephedrine hydrochloride and ephedrine sulfate is unknown. The sponsor anticipates the clinical impact will be minimal. The ACPM was requested to comment.

Indication

The sponsor has withdrawn its request for indications for shock and bronchospasm. The retained indication has wording identical to one of the indications of the currently registered product. The ACPM was asked to provide advice on whether the sponsor has provided sufficient evidence in support of this indication.

Dose

Using the typical dilution of 1:10 mL 0.9% NaCl, dilution of the giving a solution of 2.5 mg/mL. It is somewhat challenging to deliver aliquots of 3 mg or multiples thereof. As noted above the evidence to support this dosage regimen is lacking from the submission. Instructions for dilution to achieve a 3 mg/mL solution are necessary to assist the health professional administering the product, to reduce the risk of miscalculation and medication errors.

There are now no dosing instructions for the paediatric age group. The sponsor is asked to clarify if Ephedrine Hydrochloride MYX is intended for use in the paediatric age range. If so, the dosage instructions should be clearer.

Data deficiencies

Many of the references provided by the sponsor do not specifically include the use of ephedrine hydrochloride. The evidence in support of efficacy is predominantly outside the requested indication (prevention rather than treatment of hypotension induced by spinal

anaesthesia) and in a narrower population. The evidence for the proposed dosage regimen is limited.

Conditions of registration

There will be a RMP condition of registration once an RMP is agreed with the Pharmacovigilance and Special Access Branch.

Questions from the Delegate for the sponsor

1. The pharmacokinetics section contains information not included in the currently approved PI. What is the source of this information?
2. The sponsor has not included dosing instructions for children in the latest version of the PI. Please clarify whether the sponsor is seeking the proposed indication for children.
3. As the sponsor has pointed out a variety of dosage regimens including infusion, prophylactic bolus doses then small incremental doses, or incremental dosing. Please briefly summarise the evidence (clinical trials, meta-analyses) that support the efficacy and safety of the product for the proposed dosage regimen for the treatment of hypotension induced by spinal anaesthesia.

Delegate's considerations

Whether overall sufficient evidence has been provided to support the safety and efficacy of ephedrine hydrochloride.

This is a new ephedrine salt, it has 6.3% more free ephedrine (weight for weight). It has 11.2% less ephedrine when the 25 mg/mL ampoule is diluted to 1:10 with 0.9% NaCl, as is customary, before administration. The issue is whether these differences are likely to have clinical consequences given the sponsor has no data directly comparing the two salts.

The sponsor has amended its requested indications and routes of administration to limit use to 'treatment of hypotension secondary to spinal anaesthesia' and for intravenous use only. The sponsor has provided clinical data that demonstrate the use in prophylaxis and treatment of hypotension in the setting of spinal anaesthesia for caesarean section. The issue is whether this is adequate to support the more broad indication requested.

The dosage section of the PI has been revised. The issue is whether the sponsor's new dosing instructions are supported by sufficient evidence and whether the dilution recommendations are practical and provide sufficient guidance.

Whether the revision of the overdose section has retained sufficient clinical advice.

How the risk of medication errors can be managed and whether the sponsor's proposals are sufficient.

Proposed action

The Delegate was not in a position to say, at this time, that the application for Ephedrine Hydrochloride MYX should be approved for registration. The concerns relate to the strength of the evidence provided to support the ephedrine hydrochloride salt for the 'Treatment of hypotension secondary to spinal anaesthesia' and the challenges with the use of the dosing instructions.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The ephedrine hydrochloride salt contains 6.3% more free ephedrine than the approved ephedrine sulphate salt on a gram per gram basis. The proposed product is presented as 25 mg/mL. The net result of the different salt and the different strength is an 11.2% reduction in free based pre mL of product. Has the sponsor provided sufficient evidence to support the assertion that this difference is unlikely to be of clinical consequence?
2. The sponsor has replaced the currently approved dosing instructions in the PI. Please comment on the following:
 - a. The strength of the evidence to support the amended dosing instructions.
 - b. The ease of use of the dosing recommendations given the formulation contains 25 mg ephedrine hydrochloride salt and the recommended dose is multiples of 3 mg.
 - c. Whether specific dilution instructions are required
3. The sponsor has omitted paediatric dosing instructions from the PI. The sponsor has been asked to clarify whether it intends the use of Ephedrine Hydrochloride MYX to be in adults only. If this is the case, does the committee have concerns regarding off-label use given the age range of patients undergoing spinal anaesthesia may include adolescents (for example obstetrics)?
4. The sponsor has removed the clinical advice that is present in the ephedrine sulphate PI from the overdose section. Has the sponsor provided sufficient evidence or justification for removing this information?
5. The sponsor has provided proposed labels for the ampoule and carton. What additional risk minimisation strategies does the committee recommend to ensure medication errors are minimised with this product?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor would like to make the following comments:

With regard to advice sought (2b). *'The ease of use of the dosing recommendations given the formulation contains 25 mg ephedrine hydrochloride salt and the recommended dose is multiples of 3 mg'*:

The PI proposes slow IV injection of 3 to 6mg and not multiples of 3 mg as such. Further comment is made on dose multiples within the annotated PI and in later sections of this response.

With regard to advice sought(4). *The sponsor has removed the clinical advice that is present in the ephedrine sulphate PI from the Overdosage section. Has the sponsor provided sufficient evidence or justification for removing this information?*

The sponsor considered it appropriate to remove references to products no longer available on the ARTG for the treatment of overdose. No other information has been removed from the DBL PI. If the Delegate disagrees with this approach then these details can be reinserted.

With regard to the statement *'There are two registered products in Australia that contain ephedrine: Hospira Ephedrine Sulfate Injection (AUST R 224845) and DBL Ephedrine Sulfate (AUST R 16325). Both these products contain the ephedrine sulfate salt at a concentration of 30 mg /mL'*

Both Australian directors of pharmacies and anaesthetists canvassed by Mayne Pharma have expressed an interest in having an alternative supply of ephedrine injection to alleviate a reliance on a single source of this critical product in Australia and to alleviate pharmacy budget pressures. The resounding feedback to the potential introduction of Ephedrine Hydrochloride MYX 25 mg/1 mL ampoule as an alternative to the current Ephedrine Sulfate 30 mg/1 mL ampoules for the treatment of hypotension secondary to spinal anaesthesia given the difference in potency is not clinically relevant as the drug is titrated to effect has been very favourable.

Response to questions for the sponsor from the delegate

Question 1

The pharmacokinetics section contains information not included in the currently approved PI. What is the source of this information?

Sponsor's response:

The pharmacokinetic section of the PI was updated in the response to TGA consolidated questions. Mayne Pharma's response included references used in assembly of this updated pharmacokinetic detail. The second round evaluation report cited in reaction to this update, '.....the evaluator is satisfied with the response'. No further update to the pharmacokinetic section of the PI was requested.

Question 2

The sponsor has not included dosing instructions for children in the latest version of the PI. Please clarify whether the sponsor is seeking the proposed indication for children.

Sponsor's response:

Mayne Pharma is not seeking approval for the treatment of hypotension in children secondary to spinal anaesthesia. The PI has been updated accordingly.

Question 3

As the sponsor has pointed out a variety of dosage regimens including infusion, prophylactic bolus doses then small incremental doses, or incremental dosing. Please briefly summarise the evidence (clinical trials, meta-analyses) that support the efficacy and safety of the product for the proposed dosage regimen for the treatment of hypotension induced by spinal anaesthesia.

Sponsor's response:

The following response has been prepared on Mayne Pharma's behalf by [information redacted]. [Information redacted] assisted with the updates to the PI provided in the response to TGA consolidated questions and his resume is provided. The response is as follows:

'The assessor has asked for further detail to be provided with respect to clinical trial data involving ephedrine. I hope that the following information will help.

As soon as a local anaesthetic is instilled into the cerebro-spinal fluid, sympathetic outflow from the thoraco lumbar segments is essentially abolished, or at least seriously attenuated. This results in a rapid onset of significant hypotension that can place both the patient (and if they are pregnant, the fetus) at risk.

With regard to studies involving ephedrine in the treatment (as opposed to prophylaxis) of hypotension, I can provide the following information.

There have been numerous studies involving ephedrine (rarely is the nature of the salt named) and management of hypotension involving spinal anaesthesia. The papers that have been studied generally fall into three distinct categories:

1. *Studies where ephedrine is compared to phenylephrine*
2. *Studies where ephedrine and phenylephrine have been used in obstetric patients with pre-eclampsia*
3. *Studies comparing ephedrine and phenylephrine where different anaesthetic techniques have been used such as spinal versus General Anaesthesia or spinal versus combined spinal/epidural technique.*

Because of the differing end points of these studies, there have not been any useful meta-analyses available. However, in general there is a substantial amount of material that clearly demonstrates the clinical efficacy in the management of spinal anaesthesia induced hypotension. A similar finding was seen in the study by Bhardwaj et al. 2013.²⁵

One point that is clear from all studies is that the dose of ephedrine required to restore blood pressure is extremely variable. This will come as no surprise to those of us who administer the drug on a daily basis. The drug is usually administered in aliquots of 5-10 mg clinically, and after each injection the operator needs to wait 2 to 3 minutes for the next blood pressure reading to assess the response to treatment. In the articles referred to below, the TOTAL dose administered is referred to.

Ephedrine has been considered as the standard for treatment of spinal induced hypotension for over twenty years, which explains why some of the papers cited here come from the early to mid 1990's.

Van de Velde et al. 2004 was a large scale retrospective review.²⁶ They examined haemodynamic changes following neuraxial blockade. Mean ephedrine use was 14.6 ± 4.4 mg. Bhardwaj et al. 2013 a prospective study of 90 ASA 1 female patients ephedrine was administered as a 5 mg bolus, followed by an infusion of needed at 2.5 mg/min. There was minimal rebound hypertension. A second study that incorporated bolus plus infusion was that of Arago et al 2014²⁷ involving a 4 mg bolus of ephedrine followed by an infusion of 4mg/min. Ephedrine was effective in restoring systolic blood pressure to pre-treatment levels. Berends 2005²⁸ also looked at ephedrine in the management of neuraxial induced hypotension. The average dose given was 28 ± 16 mg. No adverse events reported. Other studies where ephedrine has been successfully used in the management of spinal anaesthesia induced hypotension include Clarke et al 2005²⁹ where the average use of ephedrine was 27 ± 11 mg; Dyer et al. 2003³⁰, with a mean dose of 13.7 mg; and Pierce et al 1994³¹ where ephedrine was administered in 5 mg aliquots with a mean requirement of 36.2 ± 22.7 mg. This dose range on initial inspection would appear to be in excess of what would usually be expected. However, on closer inspection it is clear that there was one patient who required approximately 100 mg total ephedrine dose. The remaining members of the study group had a mean total ephedrine dose of about 22 to 25 mg. A well conducted study was that of

²⁵ Bhardwaj N et al. A comparison of three vasopressors for tight control of maternal blood pressure during cesarean section under spinal anesthesia: Effect on maternal and fetal outcome. *Journal of Anaesthesiology Clinical Pharmacology* 2013; 29: 26-31.

²⁶ Van de Velde et al. Low-dose combined spinal-epidural anaesthesia vs. conventional epidural anaesthesia for Caesarean section in pre-eclampsia: a retrospective analysis. *European Journal of Anaesthesiology* 2004; 21: 454-459

²⁷ De Arago FF et al. Comparison of metaraminol, phenylephrine and ephedrine in prophylaxis and treatment of hypotension in cesarean section under spinal anesthesia. *Rev Bras Anestesiol.* 2014;64(5):299---306

²⁸ Berends N et al. A randomized trial comparing low-dose combined spinal-epidural anesthesia and conventional epidural anesthesia for caesarean section in severe preeclampsia. *Acta Anaesth. Belg.*, 2005; 56: 155-162

²⁹ Clark V A et al Ephedrine requirements are reduced during spinal anaesthesia for caesarean section in preeclampsia. *International Journal of Obstetric Anesthesia* 2005; 14: 9-13

³⁰ Dyer R A et al Prospective, Randomized Trial Comparing General with Spinal Anesthesia for Cesarean Delivery in Preeclamptic Patients with a Nonreassuring Fetal Heart Trace. *Anesthesiology* 2003; 99: 561-569

³¹ Pierce A T et al Effects of ephedrine and phenylephrine on maternal and fetal atrial natriuretic peptide levels during elective cesarean section. *Acta Anaesthesiol Scand* 1994; 38: 48-51.

Prakash et al 2010.³² Thirty women who underwent spinal anaesthesia were administered ephedrine in 6 mg aliquots for the management of hypotension. An average dose of 12.5 ± 5.1 mg of ephedrine was used and there were no adverse events recorded. The study of Thomas et al. (1996)³³ was also a prospective study. Ephedrine in 5 mg boluses was administered (Range 1-8 injections) to maintain systolic blood pressure in a study group of 30 participants. There were no significant adverse events reported.

In summary, the papers presented above demonstrate three main points.

1. Ephedrine has been used in clinical anaesthetic practice for over twenty five years and has stood the test of time as an effective agent in the management of spinal anaesthesia induced hypotension.
2. The dose of ephedrine needed to restore blood pressure is a very variable amount and covers a wide range. This is not at all unexpected, since management of spinal anaesthesia induced hypotension is based on empirical treatment on a case by case basis. While these studies, and published prescribing information are useful as guides, the actual dosage given and the decision as to whether this needs to be repeated, and if so, how often, will be at the discretion of the attending anaesthetist.
3. Due in part to the mode of administration, that is repeated aliquots, ephedrine is an extremely safe drug. Adverse effects are few, and when they have been reported, are transient in keeping with the pharmacokinetics of the drug.

With response to the dosage. Because of the empirical nature of the management of spinal anaesthesia induced hypotension, the final concentration of the ephedrine hydrochloride solution for administration while important, is not of critical significance. Most drugs that are used by the anaesthetist are diluted to either 5, 10 or 20 mL for convenience of calculation of the final dose.

Any suggestion that the ephedrine hydrochloride should be diluted to a final volume of 8.3 mL, thus giving an approximate concentration of 3 mg/mL, is, in my opinion unnecessary, and could indeed lead to unintentional dilution errors. I would suggest that the ephedrine hydrochloride be diluted in 10 mLs of diluent, giving a final accurate concentration of 2.5 mg/mL. The anaesthetist can adjust the volume appropriately'.

The sponsor also responded to requests regarding amendment to the PI but this is beyond the scope of the AusPAR.

Latest PSUR

As discussed by the applicant and noted by the Delegate, the proposed product has been supplied in Italy since 1993. There were no adverse events reported in the PSURs from the period December 1998 to April 2011. No further updates are currently available.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Ephedrine Hydrochloride MYX solution for

³² Prakash S et al. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: a randomised study. *International Journal of Obstetric Anesthesia* 2010; 19: 24-30.

³³ Thomas D G et al Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1996; 76: 61-65.

injection containing 25 mg/mL of ephedrine hydrochloride to have an overall positive benefit–risk profile for the amended indication;

Ephedrine Hydrochloride MYX Injection is indicated in the treatment of hypotension secondary to spinal anaesthesia.

In making this recommendation the ACPM

- was of the view that the 11.2 % difference in concentration of the base drug in ephedrine hydrochloride 25 mg/mL compared with ephedrine sulfate 30 mg/mL is not clinically significant.
- was of the view that the College of Anaesthetists should be involved in any education campaign in order to raise physicians' awareness about the difference in route of administration and strength of this new product compared with the current ephedrine sulphate products available on the Australian market.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Change the dilution directions to 25 mg in 10 mL to produce a concentration of 2.5 mg/mL.
- Change the dosing increments from 3 mg to 2.5 mg in line with the dilution directions.
- Emphasise that ephedrine hydrochloride must be diluted prior to administration for safety reasons to minimise any risk of overdose.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *The ephedrine hydrochloride salt contains 6.3% more free ephedrine than the approved ephedrine sulphate salt on a gram per gram basis. The proposed product is presented as 25 mg/mL. The net result of the different salt and the different strength is an 11.2% reduction in free based pre mL of product. Has the sponsor provided sufficient evidence to support the assertion that this difference is unlikely to be of clinical consequence?*

The ACPM advised that in the clinical setting the dose varies widely and is titrated to response. Therefore, there is little meaningful clinical significance if the two different preparations of ephedrine vary by 11.2% in concentration of the base drug. The ACPM was however of the view that it was important that this difference is highlighted on the product labelling.

2. *The sponsor has replaced the currently approved dosing instructions in the PI. Please comment on the following:*
 - a. *The strength of the evidence to support the amended dosing instructions.*
 - b. *The ease of use of the dosing recommendations given the formulation contains 25 mg ephedrine hydrochloride salt and the recommended dose is multiples of 3 mg.*
 - c. *Whether specific dilution instructions are required*

The ACPM noted that the dosing instructions in the draft PI are based on the route of administration being only intravenous (not subcutaneous, intramuscular and intravenous as with the DBL product). The ACPM noted that the recommended dosing in the draft PI

was 3 mg every 3 to 4 minutes and that the sponsor proposed the 25 mg injection be diluted to 8 mL to give an approximate concentration of 3 mg/mL (which the ACPM noted was actually 3.125 mg/mL). The ACPM was of the view that this was not practical and that it would be make more sense to make a dilution of 25 mg in 10 mL to give a concentration of 2.5 mg/mL. Therefore, dosing could be given in multiples of 2.5 mg and not 3 mg as is currently recommended in the draft PI.

The ACPM advised that specific instructions regarding dilution should be given for safety reasons.

- 3. The sponsor has omitted paediatric dosing instructions from the PI. The sponsor has been asked to clarify whether it intends the use of Ephedrine Hydrochloride MYX to be in adults only. If this is the case, does the committee have concerns regarding off-label use given the age range of patients undergoing spinal anaesthesia may include adolescents (for example obstetrics)?*

The ACPM noted the sponsor's pre-ACPM response which clarified that the use will only be in adults and that the PI has been updated accordingly. The ACPM was of the view that this was appropriate.

- 4. The sponsor has removed the clinical advice that is present in the ephedrine sulphate PI from the Overdosage section. Has the sponsor provided sufficient evidence or justification for removing this information?*

The ACPM noted that Ephedrine Hydrochloride MYX is only for intravenous administration and therefore the duration of any overdose will be short lived and self-limiting, in contrast to ephedrine given intramuscularly or subcutaneously. The ACPM advised that the risk of overdose could be minimised if the PI emphasised that ephedrine hydrochloride 25 mg/mL must be diluted before administration.

- 5. The sponsor has provided proposed labels for the ampoule and carton. What additional risk minimisation strategies does the committee recommend to ensure medication errors are minimised with this product?*

The ACPM advised that it is important that the product be clearly labelled for intravenous use only and that the sponsor should ensure that prescribers are aware that the strength and free base are different from the current products available. The ACPM noted that the sponsor proposed to raise physicians' awareness by an education campaign in the form of the distribution of posters. The ACPM advised that the College of Anaesthetists should also be involved in order to raise physicians' awareness about the difference in route of administration and strength of this new product compared with the current ephedrine sulphate products available on the Australian market.

- 6. The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

Although unrelated to the approvability of the current application, the ACPM was of the view that the PIs of the current registered ephedrine sulfate products should be reviewed and updated to reflect current clinical practice.

The ACPM advised that 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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ephedrine Hydrochloride MYX ephedrine hydrochloride 25 mg/ 1 mL injection ampoule, indicated for:

Ephedrine Hydrochloride MYX injection is indicated in the treatment of hypotension secondary to spinal anaesthesia.

Specific conditions of registration applying to these goods

The Ephedrine Hydrochloride MYX Risk Management Plan (RMP), version 1.3, dated 7 July 2016, data lock point 5 January 2016, included with submission PM-2015-01131-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Ephedrine Hydrochloride MYX approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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