Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ephedrine hydrochloride

Proprietary Product Name: Ephedrine Hydrochloride SXP /Ephedrine Hydrochloride RMB / Ephedrine Hydrochloride AJS

Sponsor: Southern Cross Pharma Pty Ltd

October 2017

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 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>.

About AusPARs

- 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.

Contents

Common abbreviations

Abbreviation	Meaning
AHFS	American Hospital Formulary Service
AHFS	American Hospital Formulary Service
ANZCA	The Australian and New Zealand College of Anaesthetists
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
BNF	British National Formulary
BP	British Pharmacopoeia
CAS	Chemical Abstracts Service
CMI	Consumer Medical Information
CNS	central nervous system
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drugs Administration
HCl	hydrochloride
IM	intramuscular
IV	intravenous
NaCl	sodium chloride
PI	Product Information
RCT	Randomised controlled trial
SC	subcutaneous
SPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration
UK	United Kingdom
USA	United States of America

Abbreviation	Meaning
USP	US Pharmacopoeial Convention

I. Introduction to product submission

Submission details

Type of submission:	Major variation (new dose form)
Decision:	Approved
Date of decision:	6 October 2016
Date of entry onto ARTG	3 March 2017
Active ingredient:	Ephedrine hydrochloride
Product names:	Ephedrine hydrochloride AJS, Ephedrine hydrochloride RMB, Ephedrine hydrochloride SXP
Sponsor's name and address:	Southern Cross Pharma Pty Ltd Suite 5 118 Church Street Hawthorn VIC 3122
Dose form:	Solution for injection
Strength:	30 mg/mL
Container:	ampoule
Pack size:	5 ampoules
Approved therapeutic use:	*Ephedrine hydrochloride is indicated in the treatment of hypotension secondary to spinal anaesthesia.*
Route of administration:	Intravenous
Dosage:	For instructions on dosage please see the Product Information.
ARTG numbers:	259539, 259692, 259672

Product background

This AusPAR describes the application by Southern Cross Pharma Pty Ltd (the sponsor) to register Ephedrine hydrochloride AJS, Ephedrine hydrochloride RMB, and Ephedrine hydrochloride SXP; ephedrine hydrochloride 30 mg/mL solution for injection for the following indication:

> *Ephedrine Hydrochloride Injection 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 Injection 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 with two chiral centres. 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 $beta_1$ and $beta_2$-adrenergic activity and has pronounced stimulating effects on the central nervous system (CNS). It has more prolonged although less potent effects than adrenaline.

Ephedrine stimulates heart rate (beta adrenergic effects) and constricts peripheral vessels variably increasing peripheral resistance. It has effects on smooth muscle, including the bladder (alfa 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.

Regulatory status

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 sulfate was 'grandfathered' on to the Australian register of therapeutic goods (ARTG).

No other ephedrine hydrochloride products are approved for use in Australia.

At the time TGA considered this application an application for a similar product was also under review[1].

Ephedrine hydrochloride is approved for use in New Zealand.

Ephedrine sulphate 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.

At the time the TGA considered this application, a similar application had been approved in (France, 2011,) and Germany (February 2013) and the United Kingdom.

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 (if applicable)

There are currently two products containing ephedrine on the ARTG (as described above). 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 tabulated below:

[1] Note a submission for a separate Ephedrine hydrochloride product had recently been assessed by the TGA and some of the issues raised in that submission were taken into consideration for this submission.

Table 1: the concentration of ephedrine free base in ephedrine hydrochloride and ephedrine sulfate

Ephedrine products	Ephedrine Sulfate	Ephedrine hydrochloride
Salt concentration	30 mg/mL	30 mg /mL
Molar ratio – salt: free base	1:2	1:1
Free base concentration[2]	(30/428.54) x 2 x 165.23 = 23.13 mg/mL	(30/201.69) x 1 x 165.23 = 24.58 mg/mL

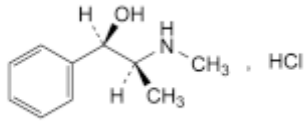
It can be seen that the amounts of ephedrine base in each of the two salts is different and on that basis, the proposed product is considered to be a new strength as it delivers approximately 5% more ephedrine (on a mg basis) per mL of solution compared to the existing (ephedrine sulfate) products. The sponsor states that the difference in potency can be considered to be minor given that the 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.

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 per cent).

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

Figure 1: Structure of ephedrine hydrochloride



Drug product

The product is a colourless solution for injection containing 30 mg/1 mL of Ephedrine hydrochloride in water. 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.

[2] Molecular weight - Ephedrine sulfate: 428.54; Ephedrine hydrochloride: 201.69; Ephedrine: 165.23

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 18 months when stored at temperatures below 25 °C is recommended for the proposed drug product.

Biopharmaceutics

Ephedrine hydrochloride is a solution for intravenous injection which is essentially similar to the existing products Hospira Ephedrine Sulfate Injection (AUST R. 224845) and DBL Ephedrine Sulfate (AUST R. 16325) by Hospira Australia Pty Ltd. 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

Provided the remaining chemistry and quality control aspects are satisfactorily resolved, registration of the product will be recommended with respect to chemistry and quality control.

III. Nonclinical findings

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. For completeness, an "Effects on Fertility" statement is also suggested for inclusion (see below). Presentations of further details regarding the nonclinical evaluation of the PI are 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 extract form the clinical evaluation report.

Introduction

Clinical rationale

The sponsor has not included a clinical rationale for the change in salt, just stated that they propose to: 'register Ephedrine Hydrochloride Injection 30 mg/mL as a generic equivalent of the reference product DBL Ephedrine sulphate injection 30 mg/mL (Hospira Australia Pty Ltd).'

The sponsor asserts that the claim for generic equivalence is based on the TGA adopted European guidance on bioequivalence[3] which states:

> *'The different salts, 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.'*

[3] CPMP/EWP/QWP/1401/98 Rev. 1- Guideline on the Investigation of Bioequivalence (January 2010)

TGA definition of generic product:

The Therapeutic Goods Regulations 1990, Schedule 9, defines a generic product as a medicine that, in comparison to a registered medicine or a medicine that has been registered but is no longer a registered medicine (previously registered medicine):

a. has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the registered medicine or previously registered medicine; and

b. has the same pharmaceutical form; and

c. is bioequivalent; and

d. has the same safety and efficacy properties.

Guidance

· Section 15.3 of Guidance 15 of the Australian regulatory guidelines for prescription medicines (ARGPM)

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

Contents of the clinical dossier

The submission contained the following clinical information:

· No clinical data submitted.

· Application letter, application form, draft Australian PI and CMI, European Summary of Product Characteristics.

· Nonclinical overview (which contained human data), Clinical Overview.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Not applicable. No sponsor initiated clinical trials were submitted as part of this application.

Pharmacokinetics

Studies providing pharmacokinetic data

No pharmacokinetic studies were submitted. In the clinical overview the sponsor states that the 'clinical pharmacology of this medicine is adequately described in the product information documents of the Australian reference product. The data supporting this has been evaluated and approved by TGA.'

For a full presentation of the PK evaluation please see Attachment 2, extract from the clinical evaluation report.

Evaluator's conclusions on pharmacokinetics

The sponsor did not provide any new pharmacokinetic data, stating that the pharmacology of ephedrine is adequately described in the PI of the Australian reference product. This is probably an acceptable argument to support intravenous administration[4] of ephedrine hydrochloride, as both the currently approved ephedrine sulfate and the proposed ephedrine hydrochloride are simple aqueous solutions containing the same active substance (ephedrine) and hence bioequivalence studies are not required. However, the sponsor has submitted an analytical report that identifies that the ephedrine hydrochloride formulation contains 6.3% more ephedrine than the currently approved ephedrine sulfate formulation. The two formulations also differ in excipient content (ephedrine sulfate contains 3 mg/mL NaCl as an excipient, and ephedrine hydrochloride contains no excipients). Therefore the rate and extent of absorption of ephedrine hydrochloride for the intramuscular or subcutaneous routes of administration may be affected, and cannot be considered to be bioequivalent to ephedrine sulfate for these routes of administration. The sponsor is required to provide data or a justification for not providing this data.[5]

Pharmacodynamics

Studies providing pharmacodynamic data

No pharmacodynamic studies were submitted. In the clinical overview the sponsor states that the 'clinical pharmacology of this medicine is adequately described in the PI documents of the Australian reference product. The data supporting this has been evaluated and approved by TGA.' The sponsor provided a nonclinical overview which also contained human data. This document presented a general review of the pharmacology and toxicology of ephedrine and relied solely on published literature (references not provided; 51 references in bibliography of which 38 appear to relate to humans). Of note, the only therapeutic indications discussed under clinical particulars in this document were those relating to the treatment of hypotension, not bronchial asthma and reversible bronchospasm, and only for the intravenous route of administration (that is consistent with the European SPC). The lack of published data for ephedrine was stated by the sponsor to be 'offset to a certain extent by its widespread and repeated use, which should be taken into account when assessing the risks linked to the current use of the substance.'

Evaluator's conclusions on pharmacodynamics

Ephedrine has been in clinical use for approximately 100 years, and the pharmacology can be considered well established. However some of the data that would be expected for more recently developed drugs is not necessarily available in the published literature. The principal issue with the new formulation of ephedrine hydrochloride is that it contains a 6.3% higher dose of ephedrine than ephedrine sulfate. No dose response data were submitted that could inform the clinical implications of this dose difference.

Dosage selection for the pivotal studies

Not applicable, no studies were submitted for evaluation.

[4] Clarification: for the IV route bioequivalence data were not required.
[5] Clarification: The quality evaluator for the original application for the current product believed that the difference in the amounts of sodium chloride (0.3%), particularly for a small volume injection, is insignificant and unlikely to affect the bioavailability of the proposed parenteral product when administered via the intramuscular and subcutaneous routes.

Efficacy

Studies providing efficacy data

No clinical data were submitted for evaluation. In the clinical overview the sponsor states that the 'efficacy of this medicine is adequately described in the product information documents of the Australian reference product. The data supporting this has been evaluated and approved by TGA.'

The only new data submitted by the sponsor was the analytical report, which has been discussed above. In justifying that ephedrine hydrochloride has the same efficacy as ephedrine sulfate, the sponsor states: '*The active moieties of EH and ES are identical that is, $C_{10}H_{15}NO$. It is reasonable to conclude the active molecules in each product will be equally well tolerated in terms of safety and efficacy*.' While this statement is true on a mg to mg basis, if ephedrine hydrochloride is used as proposed in the PI (with the same posology as ephedrine sulfate) the dose / concentration of ephedrine will be 6.3% higher than an equivalent volume of ephedrine sulfate. It is not known whether this level of increase in the dose is likely to be clinically significant, and no efficacy data was provided to address this. The efficacy implications of a higher dose are of most relevance to the first dose as further doses can be titrated against the initial patient response.

Evaluator's conclusions on efficacy

In the analytical report submitted by the sponsor it was calculated that the ephedrine hydrochloride formulation contains 6.3% more ephedrine than the currently approved ephedrine sulfate formulation. While the report concluded that the doses of ephedrine between the formulations are '*concordant …. within the permitted variations of the pharmacopoeial specifications*', the lowest and the highest permitted mass from ephedrine hydrochloride are still 6.3% higher than the lowest and the highest permitted mass from ephedrine sulfate. It is accepted that the clinical efficacy of the same dose of freebase ephedrine is the same irrespective of the salt from which it is derived, however the ephedrine hydrochloride formulation contains 6.3% more ephedrine than the currently approved ephedrine sulfate formulation and there is the potential for an increased patient response (for example over correction of low BP) to ephedrine hydrochloride if administered using the same dosing instructions as for ephedrine sulfate.

The sponsor is seeking the same indications and the same routes of administration that are approved for the ephedrine sulfate formulation in Australia. However in the European jurisdictions where ephedrine hydrochloride is approved, the only indication is to reduce hypotension during spinal anaesthesia and only the intravenous route of administration is approved. The sponsor needs to provide the rationale for these differences.

The evaluator recommends that the sponsor seek additional input from experts in adult, obstetric, and paediatric anaesthesia, emergency medicine, and hospital pharmacy to determine the clinical implications for the existence of two formulations of ephedrine, particularly with respect to the potential for dosing errors, or a greater than expected clinical response because the proposed ephedrine hydrochloride formulation contains a 6.3% higher ephedrine dose than the currently approved ephedrine sulfate formulation. Advice should also be sought from the ACPM regarding these matters.

Safety

Studies providing safety data

No clinical data were submitted for evaluation. In the clinical overview the sponsor states that the 'safety of this medicine is adequately described in the product information documents of the Australian reference product. The data supporting this has been evaluated and approved by TGA.'

The only new data submitted by the sponsor was the analytical report, which has been discussed in the pharmacokinetics section. In justifying that ephedrine hydrochloride has the same safety as ephedrine sulfate, the sponsor states: 'The active moieties of EH and ES are identical that is, $C_{10}H_{15}NO$. It is reasonable to conclude the active molecules in each product will be equally well tolerated in terms of safety and efficacy.' While this statement is true on a mg for mg basis for intravenous administration, if ephedrine hydrochloride is used as proposed in the PI (with the same posology as ephedrine sulfate) the dose / concentration of ephedrine will be 6.3% higher than an equivalent volume of ephedrine sulfate. Whether this is equally true for the SC and IM routes of administration is not known, as no data were presented to demonstrate that the rate and extent of absorption of ephedrine hydrochloride via these routes is the same as for ephedrine sulfate. Additionally, it is not known whether there are other safety implications (for example local reactions) for the SC and IM routes of administration.

It is unclear whether a 6.3% increase in the dose is likely to be clinically significant, and the sponsor has provided no safety data to address this. The safety implications of a higher dose are of most relevance to the first dose as further doses can be titrated against the initial patient response. Also, as noted, there is already a measure of inaccuracy with the dose of ephedrine administered following dilution of the drug prior to use. This inaccuracy is likely to be further increased with the 6.3% difference in dose between ephedrine hydrochloride and ephedrine sulfate if both products are available in the market. While 6.3% might be considered to be a relatively small dose difference, it may be sufficient to cause unintended consequences in some individuals (for example extremes of age, multiple medications, critical illness, etcetera.) if one formulation is mistaken for the alternative. It adds an additional factor to be considered by clinicians prior to use and may result in dosing errors, particularly in a clinical emergency.

Evaluator's conclusions on safety

The safety of the same dose of freebase ephedrine can be expected to be the same irrespective of the salt from which it is derived. However the higher dose of ephedrine in the ephedrine hydrochloride formulation compared with the currently approved ephedrine sulfate formulation has the potential to cause more adverse reactions (for example hypertension, arrhythmias, CNS stimulation, acceleration of fetal heart rate, etcetera.), if administered using the same dosing instructions as for ephedrine sulfate. If given intravenously, the dose difference between the hydrochloride and sulfate formulations is 6.3%. However the dose difference for the SC and IM routes of administration is unknown as no data on the rate or extent of absorption were provided. These dose differences may cause confusion in clinical practice and result in dosing errors with unintended clinical consequences. There is also the potential for additional safety issues (for example local reactions) with SC and IM administration that have not been explored. The evaluator recommends that the sponsor seek additional expert input regarding these safety issues as previously outlined.

First round benefit-risk assessment

First round assessment of benefits

The benefits of ephedrine hydrochloride compared with ephedrine sulfate in the currently approved indications are:

- Registration of an alternative ephedrine salt would provide an additional prescribing option.

First round assessment of risks

The risks of ephedrine hydrochloride compared with ephedrine sulfate in the currently approved indications are:

- Potential for dosage 'errors'. Although the difference in free base ephedrine between ephedrine sulfate and ephedrine hydrochloride is only 6.3% via intravenous administration, this difference may be sufficient to cause unintended consequences (safety and/or efficacy) in some individuals (for example extremes of age, multiple medications, critical illness, etcetera.) if one formulation is mistaken for the alternative.
- Actual dose difference between ephedrine sulfate and ephedrine hydrochloride given by the SC or IM route is not known as the impact of the formulation on the rate and extent of absorption was not presented. There is also the potential for additional safety issues (for example local reactions) from SC or IM use.
- Potential for an increase in adverse events because of the 6.3% increase in free base ephedrine.
- Bioequivalence has not been demonstrated for the intramuscular and subcutaneous routes of administration.
- Lack of clinical efficacy and safety data to support all the requested indications with a dose that deliver 6.3% higher amount of free base ephedrine.

First round assessment of benefit-risk balance

The benefit-risk balance of ephedrine hydrochloride, given the proposed usage, is unfavourable.

First round recommendation regarding authorisation

The evaluator is unable to recommend approval of ephedrine hydrochloride for the following reasons:

- Bioequivalence of ephedrine hydrochloride has not been demonstrated with ephedrine sulfate for the intramuscular and subcutaneous routes of administration. There are potential differences in bioavailability which have not been explored.
- In Europe, ephedrine hydrochloride is only approved for the treatment of hypotension during spinal anaesthesia, and only by the intravenous route of administration. No data has been presented to explain the differences in the requested indications and routes of administration in Australia versus those approved in Europe.
- Although the difference in free base ephedrine dose between ephedrine hydrochloride and ephedrine sulfate is not large (6.3%), no data has been submitted

to assess whether this could cause clinically significant differences in safety and/or efficacy for any of the proposed indications (treatment of shock unresponsive to fluid replacement; treatment of hypotension secondary to spinal anaesthesia; or treatment of bronchial asthma and reversible bronchospasm).

- There is potential for incorrect dosing to occur if one formulation is mistaken for the alternative. The clinical consequences of this have not been discussed (see point above).

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

For details of clinical questions raised, the sponsor's responses and the evaluation of these responses please see Attachment 2 extract from the clinical evaluation report.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ephedrine hydrochloride in the proposed usage are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions and review of the clinical evaluation advice, the risks of ephedrine hydrochloride in the proposed usage are:

- Potential for dosage errors: given that ephedrine hydrochloride in the vast majority of cases will be administered by an anaesthetist and that current clinical practice typically involves the administration of small IV boluses of 3 to 6 mg every 2 to 3 minutes titrated to clinical effect, it is considered that the 6.3% increase in free ephedrine in the first dose is unlikely to be clinically relevant in the majority of clinical situations, and subsequent doses can be managed by adjusting the volume or frequency of the boluses to obtain the desired clinical effect. For those clinical situations or patients where a small difference in dose may be more important, it is presumed that the anaesthetist will exercise due caution when selecting the dose and frequency of administration. However it is critical that appropriate initial and ongoing education of the relevant healthcare practitioners and staff managing hospital drug supplies is conducted to ensure errors in dose are prevented.
- Potential for an increase in adverse events: as mentioned above, given that use of small, frequent doses of ephedrine reflect current clinical practice, and that the majority of doses are likely to be administered by anaesthetists in controlled circumstances, adverse events should be able to be minimised and if they occur, managed promptly.
- Concerns regarding lack of clinical efficacy and safety data for all the requested indications and modes of administration can be mitigated by restricting the indication to the treatment of hypotension from spinal or epidural anaesthesia (or similar wording), and by restricting the method of administration to the intravenous route only.

Second round assessment of benefit-risk balance

The benefit-risk balance of ephedrine hydrochloride is unfavourable given the proposed usage, but would become favourable if the changes recommended below are adopted. In addition, an appropriate education program will need to be developed prior to registration.

Second round recommendation regarding authorisation

The evaluator would recommend approval of ephedrine hydrochloride for the treatment of hypotension from spinal or epidural anesthesia (or similar wording), subject to changes to the PI.

V. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan for this application.

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 southwestern North America, Europe, North Africa, South Western and Central Asia and the Western seaboard of South America. It was first isolated in 1885, and 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. 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.

It stimulates heart rate (beta adrenergic effects) and constricts peripheral vessels variably increasing peripheral resistance. It has effects on smooth muscle, including the bladder (alfa adrenergice 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.

Ephedrine is rapidly and extensively distributed throughout the body, with accumulation in the liver, lungs, kidneys, spleen and brain. The volume of distribution ranges from 122 to 320 L. Ephedrine is resistant to metabolism by monoamine oxidase and is largely excreted unchanged in the urine, together with small amounts of metabolites produced by hepatic metabolism. Ephedrine is metabolised by N-demethylation to phenylpropanolamine (norephedrine), the major metabolite. This is pharmacologically active (half-life 1.5 to 4 hours), producing central stimulant effects. Ephedrine is also deaminated, yielding benzoic acid, hippuric acid and 1-phenylpropane-1,2-diol. Up to 95% of the dose can be recovered in 24 hours with 55 to 75% as unchanged drug. The mean plasma half-life is about 6 hours (range: 3 to 11 hours). Clearance is 13.6 to 44.3 L/hour.

The urinary excretion is pH dependent; elimination is enhanced and half-life accordingly shorter in acid urine. In alkaline urine, excretion is reduced to 20 to 35% of the dose. Renal disease is likely to impair the elimination of ephedrine with a corresponding increase in half-life.[6]

There are two registered products in Australia that contain ephedrine. Both these products contain the ephedrine sulfate salt at a concentration of 30 mg/mL. Ephedrine sulfate was 'grandfathered' on to the ARTG.

Ephedrine hydrochloride is approved for use in New Zealand, and in the United Kingdom.

No other ephedrine hydrochloride products are approved for use in Australia.

Ephedrine sulphate 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.[7]

Excerpts from Guidance documents of relevance to this submission

The Therapeutic Goods Regulations 1990, Schedule 9, defines a generic product as a medicine that, in comparison to a registered medicine or a medicine that has been registered but is no longer a registered medicine (previously registered medicine):

a. has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the registered medicine or previously registered medicine; and

b. has the same pharmaceutical form; and

c. is bioequivalent; and

d. has the same safety and efficacy properties.

Section 15.3 of Guidance 15 of the ARGPM 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, e.g. 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."

Appendix II of the EU Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1 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 (e.g. 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.*

[6] US label for ephedrine sulfate

[7] Clarification: At the time this statement was made the ACPM had not considered any other submission but prior to ACPM review of this submission the committee had considered a different ephedrine hydrochloride product.

In the case of other parenteral routes, e.g. 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 pharmaceutical chemistry evaluator had no objections to the approval of the submission from a quality perspective. The evaluator noted the following characteristics of the product:

- Ephedrine hydrochloride is a white or almost white, crystalline powder or colourless crystals made by chemical synthesis. The structure contains two chiral centres.
- It is freely soluble in water and soluble in 96% ethanol.
- The final product is a colourless solution for injection containing 30 mg of ephedrine hydrochloride in water housed in Glass Type I Clear Ampoules. There are no excipients.
- A shelf-life of 18 months with the instructions 'Store below 25°C' was supported.

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.

The evaluator has noted that the sponsor has considered the difference (approximately 6.3%) in potency to be minor given its likely usage.

Nonclinical

There were no nonclinical data submitted in support of the application however the sponsor proposed changes to the 'Carcinogenicity' and 'Genotoxicity'. These changes were reviewed by the nonclinical evaluator, and amendments made based on information available in the public domain. A summary of that information follows:

- Ephedrine has been shown to cross the placenta and undergo early metabolism and/or redistribution in the foetus. Ephedrine has been associated with an increased risk of mild metabolic acidosis with increased umbilical plasma concentrations of lactate, glucose, epinephrine, and norepinephrine and greater UV PCO2, although it is uncertain whether this has the potential to affect clinical outcome on the neonate. Other studies have not demonstrated significant effects on neonatal outcomes. No change to the pregnancy category was recommended and it remains Category A.
- Ephedrine sulfate has not been shown to be genotoxic.
- Carcinogenesis studies of ephedrine were conducted by administering 0, 125, or 250 ppm of ephedrine sulfate to groups of rats and mice for 103 weeks. Neoplasms that occurred in these studies were not considered to be related to administration of the drug and there was no evidence of carcinogenicity for rats or mice of either sex receiving 125 or 250 ppm ephedrine sulfate in the diet for 2 years.

The sponsor has included the requested updates in its last iteration of the draft PI.

Clinical

This submission consisted of administrative data, and pharmaceutical chemistry (quality) data. No nonclinical or clinical data were provided.

In response to the clinical evaluation report the sponsor withdrew its request for the indications for bronchospasm and shock and withdrew its application for intramuscular and subcutaneous use.

In the second round clinical evaluation report the clinical evaluator recommended approval of Ephedrine Hydrochloride SXP for the amended indication of:

> *Treatment of hypotension from spinal or epidural anaesthesia.*

Pharmacology

The sponsor relied on the summary of the clinical pharmacology of ephedrine found in the currently registered DBL ephedrine sulfate PI.

The following was noted by the clinical evaluator regarding the formulation and pharmacology of the ephedrine hydrochloride.

- Rapid absorption after intramuscular or subcutaneous administration
- Onset of action after IM administration is 10 to 20 minutes
- The duration of pressor and cardiac responses to ephedrine is 1 hour after intravenous administration of 10 to 25 mg IM or SC 25 to 50 mg.
- Ephedrine is mostly renally excreted with a small proportion undergoing hepatic metabolism.
- The plasma half-life is 3 to 6 hours.
- Elimination half-life depends on urinary pH. Elimination is increased (and the half-life is decreased) with aciduria, and increased with alkaluria.
- Ephedrine is presumed to cross the placenta and to be excreted into breast milk.

Some differences between the registered ephedrine sulfate formulation and the proposed ephedrine hydrochloride salt were noted:

The registered formulation (ephedrine sulfate) contains 2.1 mg/mL NaCl to increase the tonicity of the solution to 338.8 mOsm/kg), whereas the ephedrine hydrochloride formulation contains water for injection only.

The sponsor has cited the British Pharmacopoeia (BP) and US Pharmacopeial Convention (USP) which state the following (for ephedrine hydrochloride and ephedrine sulfate, respectively):

- "When supplied as a ready-to-use solution, the injection complies with the following requirements. Content of ephedrine hydrochloride, $C_{10}H_{15}NO$,HCl 95.0 to 105.0% of the stated amount."
- "Ephedrine Sulfate Injection is a sterile solution of Ephedrine Sulfate in Water for Injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labelled amount of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$."

Using these permitted ranges, the range of ephedrine in both formulations is as shown in Table 2.

Table 2: Calculation of ephedrine mass (range) in ephedrine sulfate 30 mg/mL and ephedrine hydrochloride 30 mg/mL

Formulation	Mass of salt mg / mL (range)	Mass of ephedrine mg / mL (range)
Ephedrine HCl	30 (28.5 – 31.5)	24.58 (23.35 – 25.81)
Ephedrine sulfate	30 (28.5 – 31.5)	23.13 (21.97 – 24.29)

The clinical evaluator concluded that the ephedrine sulfate product and the ephedrine hydrochloride product contained different excipients[8] in addition to the increased free ephedrine in the hydrochloride salt and that, in the absence of clinical data, the two products could not be considered bioequivalent for IM and SC use and that the registration of Ephedrine Hydrochloride SXP for IM and SC use could not be supported.

The clinical evaluator considered that the products are simple aqueous solutions and, if they contained the same amount of active ingredient, could be considered bioequivalent in accordance with the guidance documents. However, the formulations do not contain the same amount of active ingredient.

Efficacy

No clinical efficacy data were submitted; instead, the sponsor relied on the clinical information in the PI of the reference product. The sponsor argued that clinical data are not necessary given both ephedrine sulfate and ephedrine hydrochloride contain the same active ingredient. The sponsor provided data to establish that the active moieties of the two products are the same, however the concentration of ephedrine in the hydrochloride product differs by 6.3% per mL and no data are submitted to provide assurance of the therapeutic equivalence in efficacy of the two products.[9]

Safety

No clinical data were submitted. The sponsor relied on the safety information described in the PI of the Australian reference product and a UK SPC for ephedrine hydrochloride. The justification was based on the same active moiety present in both products and that each product is therefore likely to have the same safety and efficacy profile. The justification did not take into account differences in local reactogenicity between the two formulations when given IM or SC and did not address clinical differences in safety relating to different total doses delivered. The sponsor has withdrawn its request for IM and SC use.

Risk management plan

No Risk Management Plan (RMP) was included in the submission.

Risk-benefit analysis

The sponsor had originally applied for registration of the new salt of ephedrine hydrochloride as a generic equivalent of the ephedrine sulfate products currently

[8] Clarification the excipient of concern is NaCL. Ephedrine sulfate contains 3 mg/mL NaCl as an excipient, and ephedrine hydrochloride contains no excipients
[9] Clarification: the TGA sought advice from two clinical experts with regard to efficacy and safety.

approved. The submission type was changed to a major variation to the existing register entry based on the new salt of ephedrine hydrochloride. The initial submission and the responses to questions did not contain any clinical data to support the safety and efficacy of ephedrine hydrochloride.

Efficacy

The therapeutic equivalence of the two ephedrine sulfate salts is predicted on the similarity of one simple aqueous solution of ephedrine with another. The HCl product however, contains 6.3% more ephedrine, undermining this assumption. No clinical data have been provided to support the therapeutic equivalence of the two ephedrine salts. Although the sponsor has withdrawn its request for the indication from bronchospasm and for IM and SC use, no clinical data have been provided to support the remaining proposed indications. Clinical data, such as from publications, reporting studies investigating the use of ephedrine hydrochloride for the proposed indication would have provided support for the sponsor's justification that the ephedrine hydrochloride can be used for the same indications as the ephedrine sulfate product.

The sponsor has changed the adult dosing instructions to reflect those of an ephedrine hydrochloride product available in the UK; however, the clinical evidence upon which these instructions are based has not been provided for review. Clinical evidence is necessary to support the safety and efficacy of the dosing instructions for ephedrine hydrochloride because the instructions differ from the currently registered product.

Safety and RMP

No clinical data have been provided to provide assurance there is no difference in safety profile between the two salts. The active moiety is the same in both and the excipients are commonly used solutions. The additional ephedrine per mL in the hydrochloride solution likely precludes the direct extrapolation of safety data from the sulfate salt. There are no clinical data to support the safety profile of the hydrochloride salt, in particular, to establish that it does not meaningfully differ from the sulfate salt. The ACPM is requested to comment on whether the differences are likely to be clinically important for the safe use of ephedrine hydrochloride.

Indication

The sponsor initially requested all the approved indications of the DBL reference product. These include the use in bronchospasm. The sponsor has subsequently amended the indications to remove this indication. It has retained the remaining indications but has proposed an extension of the indications to include the treatment of hypotension secondary to epidural anaesthesia. Although, as noted by the clinical evaluator, this is an approved indication in the UK, an extension of indication cannot immediately be granted in Australia. Clinical evidence to support the safety and efficacy of ephedrine hydrochloride for this additional indication would need to be provided in a separate submission to allow for a full evaluation.

Dose

The sponsor has made changes to the Dosage and Administration section for the use in adults following the second round evaluation report. It would appear that some of the dosing instructions are based on the UK SPC for the sponsor's UK product. In the UK the Indications do not include the use in treatment of shock unresponsive to fluid replacement. The sponsor has not provided clinical evidence to support its dosing, for either indication.

The dosing information for adults is now substantially different from the instructions of the registered product, but the paediatric dosing instructions are retained from the Australian reference product. The maximum dose is now unclear. The new dosing regimen for adults differs substantially both in dose increments and dose interval from the paediatric dosing when given for the same indication. This is not explained in the PI. The sponsor will be requested to justify its changes and provide supporting evidence in the pre-ACPM response, and the ACPM will be requested to provide advice on the acceptability of the sponsor's response.

Data deficiencies

The critical deficiency in this submission is the lack of clinical data.

The sponsor has expanded the indication in the latest version of the PI to include specific mention of the treatment of hypotension in epidural anaesthesia. The sponsor has not included clinical evidence for evaluation in the submission to support this extension of indication and it is not supported.

The uncertainties around the clinical significance of the additional 6.3% ephedrine available in the hydrochloride formulation could have been resolved with clinical data.

The sponsor's justifications for not doing so are based on the assumption the different amounts of active moiety are not sufficient for clinically meaningful effect. The ACPM will be requested to provide advice regarding the likely implications of this difference.

Conclusion

Compared to the registered ephedrine sulfate, ephedrine hydrochloride has 6.3% more free ephedrine. Although the differences in free ephedrine may seem small, an increased potency may be clinically relevant in some circumstances. The sponsor's assertion that the difference is of no concern for the safety or efficacy is not supported by any clinical data. The sponsor initially applied for all the indications and routes of administration approved for the registered product. Subsequently, the sponsor has withdrawn its request for the indication for the treatment of bronchial asthma and bronchospasm and for the IM and SC routes of administration. However, it has extended its indication to include the treatment of hypotension in epidural anaesthesia. No clinical data were provided to support the safety and efficacy of ephedrine hydrochloride for this extension of indication and it cannot be approved. The sponsor's has proposed changes to adult dosing that require clinical evidence to support their safety and efficacy.

Conditions of registration

If, post-ACPM, the submission is considered for approval the sponsor will be provided draft conditions of registration and will be invited to comment.

Questions for the sponsor

1. The sponsor has provided mock-up labels for Ephedrine Hydrochloride SXP that make reference to use intravenously, subcutaneously and intramuscularly. As the proposed route of administration is now intravenous only, the sponsor should provide updated labels for review by the TGA?
2. Please provide a brief summary of the evidence that supports the use of ephedrine hydrochloride for the treatment of shock unresponsive to fluid replacement. Please include the evidence that supports its use in both adults and children for this indication. Where evidence is lacking please justify any extrapolation made from existing evidence.

3. Please provide a brief summary of the evidence that supports the use of ephedrine hydrochloride for the treatment of hypotension secondary to spinal anaesthesia, for both adults and children. Where evidence is lacking please justify any extrapolation made from existing evidence
4. The sponsor has amended the information in the PI to align its document more closely with the EU SPC. There are, however, now differences between the EU SPC, the sponsor's proposed dosing instructions and the dosing instructions for the registered ephedrine sulfate. Please provide the following:
    a. A summary of the clinical evidence that supports the sponsor's dosing instructions. The summary should include a discussion of the evidence that supports the dosing instructions for ephedrine hydrochloride in adults for each of the requested indications (treatment of hypotension in spinal anaesthesia and the treatment of shock unresponsive to fluid replacement) should be provided separately.
    b. Please clarify the maximum dose that should be used. The introductory information states 150 mg in a 24 hours period but the adult dosage section states 30 mg is the maximum dose.

Delegate's considerations

The sponsor has made application for approval of a new salt of ephedrine hydrochloride that results in a 6.3% increase in free base compared to the registered ephedrine sulfate salt. No clinical data have been provided to support the efficacy and safety of the hydrochloride salt. The sponsor states this is unnecessary based on the likely bioequivalence of the two salts (simple aqueous solutions with the same active ingredient). It is unclear whether a direct extrapolation of the efficacy and safety profile of the approved ephedrine sulfate salt can be made given the additional potency of this salt.

The sponsor has withdrawn its request for the Indication for use in bronchospasm but has retained Indications for the treatment of shock unresponsive to fluid replacement and the treatment of hypotension secondary to spinal anaesthesia, but has extended the requested Indication to include epidural anaesthesia. No clinical data have been provided to support the extension of indication or the use of ephedrine hydrochloride in the proposed indications.

The sponsor has made changes to the Dosing and Administration section of the PI (most recent version) that differs substantially from the Dosing and Administration instructions for the currently registered product but has not provided clinical evidence to support these changes. The paediatric dosing section is unchanged from the ephedrine sulfate PI but due to the changes to the adult dosing section there are inconsistencies in this section of the PI.

No evidence is provided to support the use of ephedrine hydrochloride in children.

Proposed action

The Delegate was not in a position to say, at this time, that the application for Ephedrine Hydrochloride SXP should be approved for registration.

Request for ACPM advice

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

1. Please comment on whether a 6.3% increase in free ephedrine is likely to be clinically significant in the context of usual clinical use.

2. No clinical data have been provided. Please comment on whether an extrapolation of the safety and efficacy of the registered product is sufficient to support approval of this product.
3. The sponsor has been requested to provide a summary of the evidence to support the requested indications and for the requested populations (adults and children). Has the sponsor provided sufficient evidence to support approval of the application for each of the proposed indications in the submission and/or in its pre-ACPM response?
4. No clinical evidence to support the amended dosing instructions has been provided. The sponsor has been requested to provide clinical evidence to support the Dosing and Administration instructions.
    a. Has the sponsor provided adequate evidence to support the dosing for the requested Indications in the submission and/or in its pre-ACPM response?
    b. Can the committee comment on the adequacy of the dosing instructions for paediatric patients.

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

Table 3: Overview of changes to the submission from the sponsor

	Originally proposed	Currently proposed
Indications	*Ephedrine Hydrochloride Injection 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 Injection has also been used in the treatment of bronchial asthma and reversible bronchospasm although more selective agents (beta adrenergic agonists) are now available.*	*Ephedrine Hydrochloride Injection is indicated in the treatment of shock unresponsive to fluid replacement. It is also indicated in the treatment of hypotension secondary to spinal anaesthesia.*
Dosage and administration	Ephedrine Hydrochloride Injection is administered by the intramuscular, subcutaneous or intravenous route. Patients in shock may require intravenous administration to ensure absorption of the drug. When administered intravenously, the injection should be given slowly. Care should be taken to avoid extravasation, since this may result in tissue	Ephedrine Hydrochloride Injection is administered by the intravenous route. Patients in shock may require intravenous administration to ensure absorption of the drug. When administered intravenously, the injection should be given slowly. Care should be taken to avoid extravasation, since this may result in tissue necrosis and sloughing.

	Originally proposed	Currently proposed
	necrosis and sloughing. Ephedrine hydrochloride should be administered in the lowest effective dose. The parenteral adult dose should not exceed 150 mg in 24 hours. As a pressor: Adult dose: The usual adult dose is 25 to 50 mg (range 10 to 50 mg) administered intramuscularly or subcutaneously. Additional doses should be based on patient response. The intravenous route may be used if an immediate response is required. The dosage for the intravenous route is 10 to 25 mg which may be repeated every 5 to 10 minute until the desired response is obtained. Paediatric dose: The recommended paediatric dose is 3 mg/kg/day or 100 mg/m^2/day via the intravenous or subcutaneous route, given in 4 to 6 divided doses. During therapy with a pressor agent, blood pressure should be elevated to slightly less than the patient's normal blood pressure. In previously normotensive patients, systolic blood pressure should be maintained at 80 to 100 mmHg. In previously hypertensive patients, systolic blood pressure should be maintained at 30 to 40 mmHg below their usual blood pressure. In some patients with very severe hypotension, maintenance of even lower blood pressure may be desirable if blood or fluid volume replacement has not been completed.	Ephedrine hydrochloride should be administered in the lowest effective dose. The parenteral adult dose should not exceed 150 mg in 24 hours. As a pressor: Adult dose: The dosage for the intravenous route is 10 to 25 mg which may be repeated every 5 to 10 minute until the desired response is obtained. Paediatric dose: The recommended paediatric dose is 3 mg/kg/day or 100 mg/m^2/day via the intravenous route, given in 4 to 6 divided doses. During therapy with a pressor agent, blood pressure should be elevated to slightly less than the patient's normal blood pressure. In previously normotensive patients, systolic blood pressure should be maintained at 80 to 100 mmHg. In previously hypertensive patients, systolic blood pressure should be maintained at 30 to 40 mmHg below their usual blood pressure. In some patients with very severe hypotension, maintenance of even lower blood pressure may be desirable if blood or fluid volume replacement has not been completed.

	Originally proposed	Currently proposed
	Bronchospasm: Adult dose: The usual adult dose is 12.5 to 25 mg, given intramuscularly, subcutaneously or intravenously. Further dosage should be determined by patient's response. Paediatric dose: The usual paediatric dose is 3 mg/kg/day or 100 mg/m^2/day via the intravenous or subcutaneously, given in 4 to 6 divided doses.	

The sponsor wishes to highlight the following points which we believe are relevant to the committee's consideration of this application, and outline the information the sponsor (SCP) has previously provided to the TGA during the evaluation process.

1. *The request for advice infers that the difference in excipient content between the currently registered sulfate and proposed hydrochloride formulations of ephedrine injection will have a material effect on the tonicity of the SCP product, and therefore compromise the biowaiver which routinely applies to simple parenteral solutions. This issue is raised in the 'Background' section – parenteral solutions, and 'Clinical Evaluation' – Pharmacology of attachment 1.*

The sponsor provided both an in house assessment and published experimental data to demonstrate the small difference sodium chloride content of the sulfate and hydrochloride injections (0.3%) will have no impact on either the tonicity or viscosity of the products and therefore meet the requirements for simple parenteral solutions.

2. *The request for advice infers that the sponsor has not provided any data to support therapeutic equivalence of the sulphate and hydrochloride products, to support the conclusion that a 6.3% difference in active ephedrine between each product is not clinically relevant. This issue is raised in the 'Clinical Evaluation' – efficacy, 'Discussion' – Efficacy and 'Conclusion' sections of attachment 1.*

The TGA request for information requested SCP to provide dose response data, and discuss any implications to the efficacy and safety, relevant to the 6.3% increase in ephedrine dose associated with the administration of ephedrine hydrochloride rather than the sulfate formulation. The request for information advised that particular attention should be paid to the effect on the foetus when ephedrine is used during labour, and to the paediatric population.

The sponsor provided level I and II clinical evidence assessing mother and infant safety and efficacy dose response. The separate randomised controlled trial (RCT) was not included in the meta-analysis.

The meta-analysis demonstrated a flat dose response for hypotension and no significant dose response for hypertension following an initial dose of between 5 and 30 mg, followed up with rescue doses of 5 to 10 mg as required, depending on individual study protocols, in pregnant women prior to epidural and caesarean section. The salts of ephedrine used in the individual meta-analysed studies were not specified. The total dose range of ephedrine assessed in the meta-analysis was 0 to 47 mg. In the RCT the mean bolus and rescue dose

of ephedrine necessary to maintain BP was similar across each treatment group (16.33, 20.33 and 21 mg).

The meta-analysis concluded that the potential for benefit (correcting hypotension) equalled the risk of harm (hypertension) at an estimated dose of ephedrine of 14 mg. The RCT estimated the optimal IV bolus dose at 15 mg, based on a similar, but informal, assessment of benefit and risk.

Maternal nausea and vomiting demonstrated no relationship to the dose administered. No dose response was observed in neonate APGAR scores or umbilical pH. No significant dose response was observed in foetal acidosis. The sponsor highlighted the advice in the current ephedrine sulfate PI recommending that the dose of ephedrine when used in children should be conservatively based on response, with target pressor response based on a SBP of 80 to 100 mmHg.

3. *The request for advice does not acknowledge the requests of the clinical evaluator for PI amendments, when highlighting the inconsistencies between the sponsor's PI and the current ephedrine sulfate PI. This issue is raised in 'Questions for the Sponsor'*

In the second round recommendations provided by the clinical evaluator, following evaluation of the response to questions, it was concluded that approval would be recommended providing the sponsor restricted the indications to 'the treatment of hypotension from spinal epidural anaesthesia (or similar wording), consistent with the EU SPC'.

Further, the evaluator recommended that the IM and SC routes of administration should be removed from the PI, and doses be modified to reflect current clinical practice, 'consistent with the EU SPC for ephedrine hydrochloride'.

The sponsor modified the proposed ephedrine hydrochloride PI according to this advice. The Delegate has questioned the rationale for these changes, based on the inconsistency of the proposed PI compared to the current ephedrine sulfate PI, and because of the lack of substantiating data to support the changes.

It is the intention of the sponsor to ensure that the proposed PI is consistent with the evidence and reflective of the PI of the reference product. The table below (Table 4) compares the indications and dosage recommendations provided in the ephedrine hydrochloride SmPC, the Australian ephedrine sulfate PI and the ephedrine hydrochloride New Zealand data sheet.

Based on the evidence, the advice of the clinical evaluator and delegate, and taking into account existing product information provided in Australia, NZ and in Europe, a proposed indication and dose recommendations for the SCP injection are also provided in the table, for consideration of the Committee.

Table 4: Comparison of indications and dosage recommendations provided in the ephedrine hydrochloride SmPC, the Australian ephedrine sulfate PI and the ephedrine hydrochloride New Zealand data sheet

	Hydrochloride EU SmPC (Martindale)	Sulfate Australian PI (Hospira)	Hydrochloride NZ Data Sheet (Max Pharma)	PROPOSED SCP PI
Indication	Reversal of hypotension from spinal anaesthesia.	Treatment of shock unresponsive to fluid replacement. Treatment of	Treatment of shock unresponsive to fluid replacement. Treatment of	Treatment of shock unresponsive to fluid replacement. Treatment of

	Hydrochloride EU SmPC (Martindale)	Sulfate Australian PI (Hospira)	Hydrochloride NZ Data Sheet (Max Pharma)	PROPOSED SCP PI
		hypotension secondary to spinal anaesthesia. Treatment of bronchial asthma and reversible bronchospasm although more selective agents are now available.	hypotension secondary to spinal anaesthesia. Treatment of bronchial asthma and reversible bronchospasm although more selective agents are now available.	hypotension secondary to spinal anaesthesia.
Dosage	**Adult and the elderly** Up to 30 mg in increments of 3 to 7.5 mg. After the development of hypotension, by slow intravenous administration. Children 0.5 to 0.75 mg / kg body weight or 17 25 mg / m^2 body surface. After the development of hypotension, by slow intravenous administration.	**As a pressor** IM or SC adults 25 to 50 mg, additional doses based on response. **IV adults** 10 to 25 mg repeated every 5 to 10 minutes. **Paediatric** 3 mg/kg/day or 100 mg/m^2/day IV or SC, given in 4 to 6 divided doses. **Bronchospasm** IV, IM or SC adults 12.5 to 25 mg, additional doses based on response. Paediatric 3 mg/kg/day or 100 mg/m^2/day IV or SC, given in 4 to 6 divided doses.	**As a pressor** IM or SC adults 25 to 50 mg, additional doses based on response. **IV adults** 10 to 25 mg repeated every 5 to 10 minutes. **Paediatric** 3 mg/kg/day or 100 mg/m2/day IV or SC, given in 4 to 6 divided doses. **Bronchospasm** IV, IM or SC adults 12.5 to 25 mg, additional doses based on response. Paediatric 3 mg/kg or 100 mg/m^2 IV or SC, given in 4 to 6 divided doses.	**As a pressor** **Adults** 10 to 25 mg IV repeated every 5 to 10 minutes. **Paediatric** 3 mg/kg/day or 100 mg/m^2/day IV, given in 4 to 6 divided doses.

We believe that the SCP Ephedrine hydrochloride injection is a safe and efficacious alternative to the current sulfate formulation, when used according to the advice provided in the proposed PI. A clean and annotated copy of the proposed PI is provided.

Response to questions body of the request for ACPM advice

1. *The sponsor has provided mock-up labels for Ephedrine Hydrochloride SXP that makes reference to use intravenously, subcutaneously and intramuscularly. As the proposed route of administration is now intravenous only, the sponsor should provide updated labels for review by the TGA?*

Revised labels are included in the response.

2. *Please provide a brief summary of the evidence that supports the use of ephedrine hydrochloride for the treatment of shock unresponsive to fluid replacement. Please include the evidence that supports its use in both adults and children for this indication. Where evidence is lacking please justify any extrapolation made from existing evidence*

As outlined in the general comments above (point 2), two clinical papers were provided in response to the TGA request for information, which assessed the safety and efficacy of IV ephedrine for the prevention of hypotension during spinal anaesthesia for caesarean delivery. One paper was based on a meta-analysis of 4 RCT and one cohort study and the other on a RCT which was not included in the meta-analysis.

The evaluated and approved Australian PI and New Zealand Datasheet lists the dose for the treatment of hypotension and shock when used "as a pressor" at 10 to 25 mg IV, the approved dosage in these documents does not discriminate between the two indications, therefore as the sponsor has demonstrated clinical comparability for safety and efficacy for hypotension when used via IV injection at this specified dosage, then the demonstrated comparable safety and efficacy can be said to equally apply to the indication for shock at the identical dosage.

3. *Please provide a brief summary of the evidence that supports the use of ephedrine hydrochloride for the treatment of hypotension secondary to spinal anaesthesia, for both adults and children. Where evidence is lacking please justify any extrapolation made from existing evidence.*

As outlined in the general comments above (point 2), two clinical papers were provided in response to the TGA request for information, which assessed the safety and efficacy of IV ephedrine for the prevention of hypotension during spinal anaesthesia for caesarean delivery. One paper was based on a meta-analysis of 4 RCT and one cohort study and the other on a RCT which was not included in the meta-analysis.

Extrapolation to children is based on the approved indications and dosage recommendations for the pressor indications in the current PI, NZ data sheet and European SmPC, and the fact that both the hydrochloride and sulfate injections are simple parenteral solutions.

4. *The sponsor has amended the information in the PI to align its document more closely with the EU SPC. There are, however, now differences between the EU SPC, the sponsor's proposed dosing instructions and the dosing instructions for the registered ephedrine sulfate. Please provide the following:*

    a. *A summary of the clinical evidence that supports the sponsor's dosing instructions. The summary should include a discussion of the evidence that supports the dosing instructions for ephedrine hydrochloride in adults for each of the requested indications (treatment of hypotension in spinal anaesthesia and the treatment of shock unresponsive to fluid replacement) should be provided separately.*

As outlined in the general comments above (point 3), the sponsor modified the proposed ephedrine hydrochloride PI according to the advice provided in the second round clinical evaluation report, following evaluation of clinical data provided in response to the TGA request for information.

It is the intention of the sponsor to ensure that the proposed PI is consistent with the evidence, advice from the TGA evaluator and delegate, and reflective of the PI of the reference product. While this objective is complicated by sometimes conflicting advice, we believe the proposed indication and dose recommendations provided in the table above will provide an acceptable solution.

b. Please clarify the maximum dose that should be used. The introductory information states 150 mg in a 24 hours period but the adult dosage section states 30 mg is the maximum dose.

Please refer to the annotated PI provided.

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 SXP /Ephedrine Hydrochloride RMB / Ephedrine Hydrochloride AJS ampoule containing 30 mg in 1 ml of ephedrine hydrochloride to have an overall positive benefit–risk profile for the amended indication;

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

In making this recommendation the ACPM

- was of the view that a 6.3% increase in free ephedrine in the hydrochloride product was unlikely to be of any clinical significance, taking into account the indications for use. However, this change in formulation should be clearly stated in the product labelling and Product Information.
- noted that the sponsor failed to submit evidence to support use in other indications (epidural anaesthesia and shock unresponsive to fluid replacement) and paediatric population.

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 proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the Precautions section of the PI and relevant sections of the CMI to more accurately reflect the increased amount of free base (active drug).
- amendment of the Dosage and Administration section of the PI and relevant sections of the CMI to ensure the dosing increments are consistent with current practice.

Specific Advice

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

1. *Please comment on whether a 6.3% increase in free ephedrine is likely to be clinically significant in the context of usual clinical use.*

The ACPM was of the view that a 6.3% increase in free ephedrine is unlikely to be clinically significant. In the clinical setting dosing is usually small and repeated to effect. Dosage varies from patient to patient, and with clinical situation. However, the ACPM advised that the increased amount of free base (active drug) should be clearly stated on the product labelling and product information. Excess dose could have deleterious effects on patients such as hypertension and myocardial ischaemia or bleeding.

2. *No clinical data have been provided. Please comment on whether an extrapolation of the safety and efficacy of the registered product is sufficient to support approval of this product.*

The ACPM advised that there is sufficient evidence to support registration. The common active component (ephedrine) is the same as the long-registered ephedrine sulfate (albeit at slightly higher concentration). Both products are aqueous formulations with no significant difference in tonicity or viscosity, appropriate for intravenous therapy. However, there was no safety or pharmacokinetic data to support other routes of administration (subcutaneous or intramuscular).

3. *The sponsor has been requested to provide a summary of the evidence to support the requested indications and for the requested populations (adults and children). Has the sponsor provided sufficient evidence to support approval of the application for each of the proposed indications in the submission and/or in its pre-ACPM response?*

The ACPM was of the view that there was not sufficient evidence to support all the requested indications and populations. Based on the evidence provided, indication should only be for the treatment of hypotension due to spinal anaesthesia in adult patients. The sponsor did not submit data to support use in epidural anaesthesia, shock unresponsive to fluid replacement or use in paediatric populations.

4. *No clinical evidence to support the amended dosing instructions has been provided. The sponsor has been requested to provide clinical evidence to support the Dosing and Administration instructions.*

    a. *Has the sponsor provided adequate evidence to support the dosing for the requested Indications in the submission and/or in its pre-ACPM response?*

The ACPM advised that dosing should be consistent with usual clinical practice and the adult posology included on the UK/EU Product Information:

"Up to 30 mg in increments of 3 to 7.5 mg after the development of hypotension by slow intravenous administration."

    b. *Can the committee comment on the adequacy of the dosing instructions for paediatric patients*

The ACPM considered that the paediatric dose in the PI is not consistent with usual clinical practice and likely to be excessive. Furthermore the committee advises that this product is not recommended for use in children due to insufficient data on efficacy, safety and dosage recommendations.

5. *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.*

The ACPM noted that in the Contraindications section the PI states: "Ephedrine sulfate is contraindicated in patients undergoing general anaesthesia with cyclopropane or halothane or other halogenated hydrocarbons, since anaesthesia may increase cardiac irritability which may lead to arrhythmias." The ACPM considers that this statement is no longer relevant and it could be removed since these anaesthetic agents are no longer marketed or available.

Currently, PI states the following under the Patient monitoring section: "Cardiovascular parameters, including blood pressure ECG, cardiac output, central venous pressure and pulmonary artery pressure should be monitored during therapy with ephedrine. Urinary output should also be monitored." The ACPM suggested changing it to: "Cardiovascular parameters, including blood pressure should be monitored during therapy with ephedrine. Urinary output should also be monitored".

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 these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of:

- Ephedrine Hydrochloride AIS ephedrine hydrochloride 30 mg/mL solution for injection ampoule
- Ephedrine Hydrochloride SXP ephedrine hydrochloride 30 mg/mL solution for injection ampoule
- Ephedrine Hydrochloride RMB ephedrine hydrochloride 30 mg/mL solution for injection ampoule

Indicated for:

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

Attachment 1. Product Information

The PI for Ephedrine Hydrochloride SXP 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>. The PI for other trade names (Ephedrine Hydrochloride AIS and Ephedrine Hydrochloride RMB) is identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

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