Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ephedrine hydrochloride

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

Sponsor: Southern Cross Pharma

First round report 27 November 2015

Second round report 3 March 2016

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

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List of 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
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

1. Introduction

This is a major variation submission to register a new formulation (salt) of ephedrine: ephedrine hydrochloride rather than the currently approved ephedrine sulfate (the nominated reference product). In the pre-submission planning form the submission had been nominated as a new generic medicine application. However in the planning letter (dated July 13, 2015) the TGA advised the sponsor that:

> *The submitted formulation (ephedrine hydrochloride) is a different salt of ephedrine and contains a different amount of free ephedrine than the reference product. It is therefore not considered a generic since it does not contain the same quantitative composition of therapeutically active substances.*
>
> *You must provide either clinical data to support the indications using this new strength, or a justification for not submitting clinical data. The safety and efficacy implications of the higher amount of ephedrine need to be assessed.*

The sponsor agreed to amend the application type, and is '*requesting a confirmation of bioequivalence to the stated reference product at the conclusion of evaluation based on sound scientific rationale outlined in the Clinical Summary*.'

Evaluator's comment: Both the FDA and EMA (Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) consider that drug products that contain the same therapeutic moiety, but 'with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength' are pharmaceutical alternatives. In the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations, published by the FDA) pharmaceutical alternatives are not considered to be therapeutically equivalent.

Additional relevant FDA, EMA and TGA definitions were provided.

[Information redacted]

1.1. Drug class and therapeutic indication

From DBL Ephedrine Sulfate injection PI (the nominated reference product, hereafter referred to as ephedrine sulfate).

Ephedrine is a sympathomimetic which stimulates both alpha and beta adrenergic receptors, and also releases noradrenaline from storage site. The main effects of therapeutic doses of ephedrine are relaxation of bronchial smooth muscle, cardiac stimulation and increased systolic and usually diastolic blood pressure via an increase in cardiac output and peripheral vasoconstriction. Ephedrine also decreases intestinal tone and motility, relaxes the bladder wall, contracts the sphincter muscle, relaxes the detrusor muscle, and decreases uterine activity. Ephedrine also has central nervous system stimulant effects. Tachyphylaxis to the effects of ephedrine may also occur after use for a short while possibly due to the depletion of noradrenaline stores.

The approved ephedrine sulfate indications are:

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

The proposed indications (based on the proposed PI and Cover Letter) for ephedrine hydrochloride are identical to those registered for DBL Ephedrine Sulphate 30mg/mL, except for the replacement of 'ephedrine sulfate' with 'ephedrine hydrochloride'.

Comment: It should be noted that in the clinical overview, the sponsor states that the proposed therapeutic indications are:

- *Prevention and treatment of hypotension induced by general, spinal or epidural anaesthesia during surgery or delivery*
- *Initial treatment of hypotension occurring during shock*

Ephedrine hydrochloride is not registered or available in the USA; ephedrine sulfate is available, but not approved by the FDA. In Europe only ephedrine hydrochloride is registered, but only for the treatment of hypotension during spinal anaesthesia. The sponsor will be asked for clarification regarding the difference between the indications approved in Europe compared with the indications sought in Australia.

1.2. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

- Ephedrine Sulfate Injection 30 mg/mL

The mass of ephedrine per 30mg of the ephedrine salt is 23.13 mg.[1]

The submission proposes registration of the following dosage forms and strengths:

- Ephedrine Hydrochloride Injection 30 mg/mL

The mass of ephedrine per 30mg of the ephedrine salt is 24.58 mg.[1]

Comment: Of note, when discussing drug class, pharmacology, efficacy, safety, etcetera most references (including published articles, drug databases and the reference product PI) accessed by the evaluator discussed these issues in terms of the dose of ephedrine (the free base) rather than the particular salt. Although no specific reference could be found to confirm this, the consensus appears to be that only the dose of free base ephedrine in the formulation is relevant to safety and efficacy, not the salt from which it is derived. Based on the respective mass of ephedrine per 30 mg of the ephedrine salt, the proposed product contains 6.3% more ephedrine than the reference product.

1.3. Dosage and administration

The sponsor does not propose to change the Dosage and Administration section of the reference product PI with the exception of replacing 'Sulfate' with 'Hydrochloride'.

From Ephedrine Hydrochloride AJS/SXP/RMB Injection PI:

'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 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.'

[1] Analytical report. Commissioned by Southern Cross Pharma. December 2014. [Information redacted], Chemical Analysis Pty Ltd. Dated: 15 July 2015. This report is discussed in the pharmacokinetics section..

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/m2/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.

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 administered intravenously or subcutaneously, given in 4 to 6 divided doses.

Compatibilities

Ephedrine hydrochloride is reported to be compatible with 0.9% sodium chloride, lactated Ringer's injection, and 10% glucose in water.

Incompatibilities

Ephedrine hydrochloride is reported to be physically incompatible with the phenobarbitone sodium, pentobarbitone sodium, quinalbarbitone sodium and thiopentone sodium, and with hydrocortisone sodium succinate in some infusion solutions.

Comment: The evaluator has consulted multiple drug databases in relation to the dosing of ephedrine (Martindale, Drugs.com, American Hospital Formulary Service [AHFS], British National Formulary [BNF], UpToDate [drug information from Lexicomp]). Where both salts were listed, no distinction was made between them (the term ephedrine was used rather than the specific salt) with respect to uses, safety, or dosage and administration.

The dosage and administration sections from a representative USA label (ephedrine sulfate) and UK SPC (ephedrine hydrochloride) are compared to the Australian reference product PI in Table 1. The Dosage and Administration section of the Australian PI for DBL ephedrine sulfate is generally consistent with the US label for ephedrine sulfate, although the Australian PI contains more detailed information. The UK SPC for ephedrine hydrochloride is also generally consistent with regard to doses, although only intravenous administration is approved and only for the treatment of hypotension during spinal anaesthesia, not for shock unresponsive to fluid replacement, or asthma and reversible bronchospasm.

An important aspect of treatment with ephedrine is that the dose should be titrated according to patient response. This should reduce any potential risk associated with repeat doses; however, a 6.3% increase in the initial dose of ephedrine may have safety and efficacy implications particularly in susceptible adults and the paediatric population. It is possible that these effects may vary with the different routes of administration (that is SC, IM and IV). Adverse effects could include excess adrenergic activity resulting in hypertension, arrhythmias, CNS stimulation, acceleration of fetal heart rate, local reactions, etcetera.

Ephedrine is usually diluted prior to administration. The Australian and New Zealand College of Anaesthetists (ANZCA) published an article in Australian Anaesthesia 2013[2] that stated:

Furthermore, it has been shown variability exists in the intended drug concentration and the actual (measured) concentration of drugs used in anaesthetic practice. A study by Stucki et al,[3] showed 29% of evaluated syringes contained drug concentrations outside the designated range of acceptability (± 10% of the targeted concentration). Of concern, 18% of preparations deviated from the declared dose by ± 20% and 4% deviated by ± 100% (implying calculation or preparation error rather than technique error). The nature of preparation of ephedrine and metaraminol lends these drugs to such concentration variations. It has not been shown that pharmacy preparation is more or less accurate than anaesthetist preparation, though the lack of time pressure in the non-theatre environment is likely to equal or improve upon in-theatre dilution accuracy.

There is therefore already a measure of inaccuracy with ephedrine dose following dilution in clinical practice, and this variability will be further increased with the 6.3% change in dose between ephedrine hydrochloride and ephedrine sulfate. The implications this has for safety and efficacy need to be quantified by the sponsor, particularly in relation to the initial dose of ephedrine administered as later doses can be titrated based on patient response.

Table 1: Summary of dosage and administration from representative overseas PIs in comparison to Australian reference product PI

	Ephedrine sulfate injection, solution (Sandoz Inc)	Ephedrine Hydrochloride Injection 30 mg in 1 ml (Martindale Pharmaceuticals Ltd)	DBL Ephedrine sulfate (Hospira Australia Pty Ltd)
Version	Viewed on dailymed.nlm.nih.gov Label last updated 5/2010	Last Updated on eMC 2 January 2015	Version 5.0
Country	USA	UK	Australia
Salt (strength)	Ephedrine sulfate	Ephedrine hydrochloride	Ephedrine sulfate

[2] Goodrick, N. Pre-filled emergency drugs: The introduction of pre-filled metaraminol and ephedrine syringes into the main operating theatres of a major metropolitan centre. Australian Anaesthesia 2013; 127–134.
[3] Stucki C et al Accuracy of preparation of i.v. medication syringes for anaesthesiology. Am J Health Syst Pharm 2013; 2: 137-142

	Ephedrine sulfate injection, solution (Sandoz Inc)	Ephedrine Hydrochloride Injection 30 mg in 1 ml (Martindale Pharmaceuticals Ltd)	DBL Ephedrine sulfate (Hospira Australia Pty Ltd)
	(50mg/mL)	(30mg/mL)	(30mg/mL)
Indications	Ephedrine Sulfate Injection, USP is indicated primarily to counteract the hypotensive effects of spinal or other types of nontopical conduction anaesthesia. It is also useful as a pressor agent in hypotensive states following sympathectomy, or following overdosage with ganglionic-blocking agents, antiadrenergic agents, veratrum alkaloids or other drugs used for lowering blood pressure in the treatment of arterial hypertension. The drug is sometimes injected to relieve acute bronchospasm, but it is less effective than epinephrine for this purpose.	To reduce hypotension during spinal anaesthesia.	DBL Ephedrine Sulfate 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. DBL Ephedrine Sulfate Injection has also been used in the treatment of bronchial asthma and reversible bronchospasm although more selective agents (beta adrenergic agonists) are now available.
General dosage instructions	Depending on the clinical circumstances, Ephedrine Sulfate Injection may be given subcutaneously, intramuscularly or intravenously.	NA	DBL Ephedrine Sulfate 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 necrosis and sloughing. Ephedrine sulfate should be administered in the lowest effective dose. The parenteral adult dose should not exceed 150 mg in 24 hours.

	Ephedrine sulfate injection, solution (Sandoz Inc)	Ephedrine Hydrochloride Injection 30 mg in 1 ml (Martindale Pharmaceuticals Ltd)	DBL Ephedrine sulfate (Hospira Australia Pty Ltd)
Adult dose for hypotension	25 to 50 mg (range 10 to 50 mg) injected subcutaneously or intramuscularly (equivalent to 0.2 to 1.0 mL of 5% solution) is usually adequate to prevent or minimize hypotension secondary to spinal anaesthesia. Repeat doses should be governed by blood pressure response	Up to 30 mg in increments of 3 to 7.5 mg. After the development of hypotension, by slow intravenous administration.	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. 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.
Adult dose for bronchospasm	As above. Repeat doses should be governed according to the degree of improvement. In acute attacks of asthma, the smallest effective dose should be used (usually 0.25 to 0.5 mL) or as	NA	The usual adult dose is 12.5 to 25 mg, given intramuscularly, subcutaneously or intravenously. Further dosage should be determined by patient's

	Ephedrine sulfate injection, solution (Sandoz Inc)	Ephedrine Hydrochloride Injection 30 mg in 1 ml (Martindale Pharmaceuticals Ltd)	DBL Ephedrine sulfate (Hospira Australia Pty Ltd)
	otherwise determined by the patient's response.		response.
Hypotension during labour	When used during labour, administer only sufficient dosage to maintain blood pressure at or below 130/80.	As for adult hypotension.	As for adult hypotension.
Paediatric dose for hypotension	750 micrograms per kg of body weight or 25 mg/ m^2 of body surface injected intravenously or subcutaneously, four times daily or as otherwise determined by the patient's response.	0.5 to 0.75 mg / kg body weight or 17 to 25 mg / m^2 body surface. After the development of hypotension, by slow intravenous administration.	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.
Paediatric dose for bronchospasm	As above.	NA	The usual paediatric dose is 3 mg/kg or 100 mg/m^2 intravenously or subcutaneously, given in 4 to 6 divided doses.

2. 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 30mg/mL as a generic equivalent of the reference product DBL Ephedrine sulphate injection 30mg/mL (Hospira Australia Pty Ltd).'

The sponsor asserts that the claim for generic equivalence is based on the TGA adopted European guidance on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) 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.'*

Comment: As previously discussed above, because ephedrine hydrochloride contains a different amount of free ephedrine than the reference product, it is not considered a generic medicine. Despite agreeing to amend the application type, the sponsor has not updated the dossier to reflect this. See also the TGA definition of a generic product (below).

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.

3. Contents of the clinical dossier

3.1. Scope 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.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

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

4. Pharmacokinetics

4.1. 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.'

4.2. Summary of pharmacokinetics

The information in the following summary is extracted from the PI:

Ephedrine is rapidly absorbed after intramuscular or subcutaneous administration. The onset of action after intramuscular administration is 10 to 20 minutes, and the duration of pressor and cardiac responses to ephedrine is 1 hour after intravenous administration of 10 to 25 mg or intramuscular or subcutaneous administration of 25 to 50 mg. 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 the half-life is decreased) with decreasing pH of the urine. Ephedrine is presumed to cross the placenta, and to be excreted into breast milk.

4.3. Bioequivalence to relevant registered products

The sponsor did not conduct any biopharmaceutic studies. This was based on Guidance 15 of the ARGPM (Version 1.1 April 2015) and the EU Guideline on the Investigation of Bioequivalence.

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, 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.'*

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 (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.

Both the currently approved ephedrine sulfate and the proposed ephedrine HCl are simple aqueous solutions. Ephedrine sulfate contains only NaCl as an excipient, and ephedrine HCl contains no excipients.

4.3.1. Active substance

The sponsor commissioned an analytical report from Chemical Analysis Pty Ltd, an Australian contract chemical testing firm, 'to evaluate the case for the proposed product to meet the definition of a generic product'.[1] This report calculated the concentration of the active ingredient, ephedrine, in both formulations (Table 2).

Table 2: Calculation of ephedrine mass and concentration in ephedrine sulfate 30 mg/mL and ephedrine hydrochloride 30 mg/mL

Component	Molecular Weight	Mass Ephedrine per 30 mg (mg)*	Millimoles Ephedrine per 1.00 mL	Mass Salt per 30 mg (mg)
Ephedrine ($C_{10}H_{15}NO$)	165.23	30.00	0.182	0.00
Ephedrine HCl ($C_{10}H_{15}NO.HCl$)	201.70	24.58	0.149	5.42 (as HCl)
Ephedrine Sulfate ($[C_{10}H_{15}NO]_2.H_2SO_4$)	428.54	23.13	0.140	6.87 (as H_2SO_4)

* mass of ephedrine in the salt calculated as follows: ((MWt of ephedrine*No. of moles of ephedrine)/MWt of ephedrine salt)*30

Based on these calculations, the percentage of ephedrine in the ephedrine hydrochloride formulation relative to the reference product, ephedrine sulfate, is:

(100 x 24.58) ÷ 23.13 = 106.3%

Therefore, the proposed product (ephedrine hydrochloride) has a 6.3% higher concentration and delivers a 6.3% higher dose of ephedrine than the currently approved product (ephedrine sulfate), per mL injected.

The report then referred to the British Pharmacopoeia (BP) and US Pharmacopoeial Convention (USP) which state (for ephedrine hydrochloride and ephedrine sulfate, respectively) that:

'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% and not more than 105.0%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 3.

Table 3: 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 report concluded that: 'The two formulations are concordant for the level of ephedrine base within the permitted variations of the pharmacopoeial specifications for ephedrine sulfate and hydrochloride.'

4.3.2. Excipients

Ephedrine sulfate contains 3 mg/mL sodium chloride (NaCl) as an excipient (to achieve isotonicity) and ephedrine HCl contains no excipients. The analytical report stated that NaCl is 'widely used in a variety of pharmaceutical products to produce isotonic solutions', and, as an excipient, 'may be regarded as nontoxic and non-irritant'.[4] The amount of NaCl required to be added to a solution of ephedrine sulfate and ephedrine hydrochloride to make them isotonic was calculated, which showed that 2.1 mg/mL NaCl was needed for ephedrine sulfate (tonicity of 338.8 mOsm/kg H_2O) versus 0.3 mg/mL for ephedrine hydrochloride (although batch analysis results for ephedrine hydrochloride demonstrated isotonicity without added NaCl, tonicity range 274 - 278 mOsm/kg H_2O). The report concluded that 'the absence of NaCl in the proposed formulation is not likely to impact bioequivalence or clinical safety/efficacy for any of the routes of administration that is, IV, IM and SC [5,] and its absence is justified.'

Comment: While it is correct to state that the mass of ephedrine derived from ephedrine HCl could be consistent with the mass of ephedrine derived from ephedrine sulfate

[4] http://www.drugs.com/inactive/sodium-chloride-317.html. Accessed 20/11/2015.
[5] Therapeutic Goods Administration, Outcome of PPF assessment Letter, PM-2014-01323-1-3, dated 10th June 2014.

based on the permitted range, 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. This 6.3% higher dose / concentration does not constitute 'the same concentration' with respect to Guidance 15 of the ARGPM, and therefore biopharmaceutic data or a justification for not providing this data are required for the intramuscular and subcutaneous routes of administration. Biopharmaceutic data is not required for the intravenous administration as per Guidance 15 of the ARGPM. The difference in excipients (NaCl) is not considered clinically relevant when administered intravenously as ephedrine is usually diluted (often with normal saline [0.9% w/v NaCl]) prior to administration. However, the effect of a reduction in NaCl on the viscosity (as opposed to the tonicity) of ephedrine hydrochloride and the potential impact this has on the pharmacokinetics of the active substance when administered via the intramuscular or subcutaneous route needs to be addressed by the sponsor.

4.4. Evaluator's overall 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[6] 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.[7]

5. Pharmacodynamics

5.1. 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

[6] Clarification: for the IV route bioequivalence data were not required

[7] 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.

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.'

Comment: No literature search strategy was provided by the sponsor, so it is not known if the references used in the review are representative of the published data. References reporting human data in the sponsor's review were generally quite dated (publication year ranged from 1945 to 1999) and with the exception of 1 publication[8] which (according to the sponsor) specifically mentioned ephedrine hydrochloride, all apparently referred to 'ephedrine' rather than a specific salt. Where doses were quoted, it was not specified if this was for the free base or the salt. In addition, there was no comparison of pharmacodynamics between the different salts. For these reasons, the individual references were not requested for evaluation. Overall, the pharmacodynamic data presented were consistent with the information contained in the current approved PI for ephedrine sulfate. However, this PI is not consistent with the current Form for Providing Product Information, particularly in relation to the Precautions section (effects on fertility, use in lactation, paediatric use, use in the elderly, genotoxicity, carcinogenicity etcetera) and the absence of a Clinical Trials section. If approved for registration, the PI for ephedrine hydrochloride will need to comply with the current Form for Providing Product Information. This may require the evaluation of additional data not included in the current application.

5.2. Summary of pharmacodynamics

The information in the following summary is extracted from the PI:

Ephedrine is a sympathomimetic which stimulates both alpha and beta adrenergic receptors, and also releases noradrenaline from storage site. The main effects of therapeutic doses of ephedrine are relaxation of bronchial smooth muscle, cardiac stimulation and increased systolic and usually diastolic blood pressure via an increase in cardiac output and peripheral vasoconstriction. Ephedrine also decreases intestinal tone and motility, relaxes the bladder wall, contracts the sphincter muscle, relaxes the detrusor muscle, and decreases uterine activity. Ephedrine also has central nervous system stimulant effects. Tachyphylaxis to the effects of ephedrine may also occur after use for a short while possibly due to the depletion of noradrenaline stores.

5.3. Evaluator's overall 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.

6. Dosage selection for the pivotal studies

Not applicable, no studies were submitted for evaluation.

[8] Radstrom M, et al. Effects of ephedrine on oxygen consumption and cardiac output *Acta Anaesthesiol. Scand.* 1995; 39: 1084-1087.

7. Clinical efficacy

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.

7.1. Evaluator's conclusions on clinical 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.

8. Clinical safety

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.

8.1. Evaluator's overall conclusions on clinical 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.

9. First round benefit-risk assessment

9.1. 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.

9.2. 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.

9.3. First round assessment of benefit-risk balance

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

10. 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).

11. Clinical questions

11.1. Additional expert input

It is recommended that the sponsor seeks additional input from experts in adult and paediatric anaesthesia, emergency medicine, and hospital pharmacy to determine the clinical implications (safety and efficacy) for the existence of two formulations of ephedrine.

11.2. Clinical questions

11.2.1. Pharmacokinetics

1. In Europe it appears that the ephedrine hydrochloride formulation was the innovator product (Ephedrine Aguettant 30 mg/ml, solution for injection) and therefore only an abridged application would have been required to register a generic product in Europe. Please confirm whether any additional data (in particular any clinical data) was required to support these submissions.
2. In the clinical overview it states that 'the absence of NaCl in the proposed formulation is not likely to impact bioequivalence or clinical safety/efficacy for any of the routes of administration that is, IV, IM, and SC, and its absence is justified'. However, the effect of a reduction in NaCl on the viscosity (as opposed to the tonicity) of ephedrine hydrochloride and the potential impact this has on the pharmacokinetics of the active substance (for example rate and extent of absorption) when administered via the IM or SC route has not been discussed. Please provide data on the pharmacokinetics of ephedrine hydrochloride and its bioequivalence with ephedrine sulfate from administration via the IM and SC routes.

11.2.2. Pharmacodynamics

3. Please provide evidence of the dose response of ephedrine when given in the recommended dose range after intravenous, intramuscular or subcutaneous injections. Discussion should include the clinical implications of the 6.3% increase in ephedrine dose associated with ephedrine hydrochloride compared with ephedrine sulfate (see Question 5, below).

11.2.3. Efficacy

4. In Europe ephedrine hydrochloride is registered only for the treatment of hypotension during spinal anaesthesia, not for the treatment of shock unresponsive to fluid replacement, or for bronchial asthma and reversible bronchospasm. Please provide the rationale for the difference between the indication approved in Europe compared with the indications sought in Australia.
5. There is a 6.3% increase in the dose of ephedrine with ephedrine hydrochloride compared with ephedrine sulfate. Please provide data which quantifies the implications this has for efficacy for each mode of administration (IV, IM, SC) and for each indication, particularly in relation to the initial dose of ephedrine administered as later doses can be titrated based on patient response. Particular attention should be paid to the effect on the foetus when ephedrine is used during labour, and to the paediatric population.

11.2.4. Safety

6. There is a 6.3% increase in the dose of ephedrine with ephedrine hydrochloride compared with ephedrine sulfate. Please provide data which quantifies the implications this has for safety for each mode of administration (IV, IM, SC) and for each indication, particularly in relation to the initial dose of ephedrine administered as later doses can be titrated based on

patient response. Particular attention should be paid to the effect on the foetus when ephedrine is used during labour, and to the paediatric population.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Pharmacokinetics question 1

In Europe it appears that the ephedrine hydrochloride formulation was the innovator product (Ephedrine Aguettant 30 mg/ml, solution for injection) and therefore only an abridged application would have been required to register a generic product in Europe. Please confirm whether any additional data (in particular any clinical data) was required to support these submissions.

Sponsor response:

The sponsor stated that the submission in Europe did not contain additional clinical data to support the submission.

Evaluation of the response:

The response is noted.

12.1. Pharmacokinetics question 2

In the clinical overview it states that 'the absence of NaCl in the proposed formulation is not likely to impact bioequivalence or clinical safety/efficacy for any of the routes of administration that is, IV, IM, and SC (5), and its absence is justified'. However, the effect of a reduction in NaCl on the viscosity (as opposed to the tonicity) of ephedrine hydrochloride and the potential impact this has on the pharmacokinetics of the active substance (for example rate and extent of absorption) when administered via the IM or SC route has not been discussed. Please provide data on the pharmacokinetics of ephedrine hydrochloride and its bioequivalence with ephedrine sulfate from administration via the IM and SC routes.

Sponsor response:

The sponsor provided data on changes in viscosity of aqueous sodium chloride solutions across a concentration range of 0 to 6 molal (approximately 35%) based on experimental results obtained by Kestin (1981)[9] and across a concentration range of 0.10% to 26.3% w/w[2] (Simion 2015)[10]. Both sources show that viscosity changes very little (approximately 40 micropascal/s between a 0.0% and 2.90% concentration of NaCl at 20°C; < 0.1 millipascal/s between a 0.1% and 2.90% concentration of NaCl at 20°C, respectively). They further stated that even a NaCl concentration of 30% has a dynamic viscosity less than twice that of water. Based on the minimal impact on viscosity, they stated that 'neither the rate nor extent of absorption of ephedrine will differ, for either formulation, when administered by the IM or SC route. Further demonstration of bioequivalence is not required.'

Evaluation of the response:

[9] Kestin J, et al Tables of the dynamic and kinematic viscosity of aqueous NaCl solutions in the temperature range 20-150°C and the pressure range 0.1-35 MPa. *Journal of Physical and Chemical Reference Data* 1981; 10: 71-87.
[10] Simion AI, et al. Mathematical modelling of density and viscosity of NaCl aqueous solutions. *Journal of Agroalimentary Processes and Technologies* 2015; 21: 41-52.

The response is noted. However, given the lack of pharmacodynamic and clinical data for the IM and SC routes of administration (see answer to Question 5 below) and that ephedrine HCL registered in Europe[11] is only approved for use 'solely by or under the supervision of the anaesthetist as an injection via intravenous route', it is recommended that only the IV route of administration is approved. Based on the expert clinical advice received by the TGA, it also appears that the IV route of administration accounts for the vast majority of use of ephedrine in anaesthesia.

12.2. Pharmacodynamics question 3

Please provide evidence of the dose response of ephedrine when given in the recommended dose range after intravenous, intramuscular or subcutaneous injections. Discussion should include the clinical implications of the 6.3% increase in ephedrine dose associated with ephedrine hydrochloride compared with ephedrine sulfate (see Question 5, below).

Sponsor response:

The sponsor provided the response in a combined answer to Question 5, below.

12.3. Efficacy question 4

In Europe ephedrine hydrochloride is registered only for the treatment of hypotension during spinal anaesthesia, not for the treatment of shock unresponsive to fluid replacement, or for bronchial asthma and reversible bronchospasm. Please provide the rationale for the difference between the indications approved in Europe compared with the indications sought in Australia.

Sponsor response:

The sponsor stated that their original application was intended to be a Type D New Generic Product Application with Ephedrine Sulfate as the reference product and that the PI was based on the reference product PI. They further stated that:

'The provided clinical responses and generated data to support the contention that the proposed product is, to all intents and purposes, a generic equivalent of the reference product, suggests a rationale for differences to the European indications is not entirely relevant to the context of the application. The sponsor has based the application on both formulations being generic equivalents and the Indications in the PI reflect this.'

Evaluation of the response:

This response is not considered acceptable. The sponsor was advised in the Planning Letter (dated July 13, 2015) that as ephedrine hydrochloride is a different salt and contains a different amount of free ephedrine, it is not considered a generic of ephedrine sulfate. Therefore the indication(s) need to be justified, including differences between the approved indications in Europe compared with those sought in Australia. In the absence of such justification, it is recommended that only an indication consistent with that approved in Europe ('Treatment of hypotension from spinal or epidural anaesthesia') is approved.

12.4. Efficacy question 5

There is a 6.3% increase in the dose of ephedrine with ephedrine hydrochloride compared with ephedrine sulfate. Please provide data which quantifies the implications this has for efficacy for each mode of administration (IV, IM, SC) and for each indication, particularly in relation to the

[11] SPC Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe. Last Updated on eMC 02-Nov-2015 Aguettant Ltd

initial dose of ephedrine administered as later doses can be titrated based on patient response. Particular attention should be paid to the effect on the foetus when ephedrine is used during labour, and to the paediatric population.

Sponsor response:

The sponsor only provided data related to intravenous ephedrine doses used in the prevention of hypotension during spinal anaesthesia prior to caesarean delivery.[12, 13]

Lee (2004) was a meta-analysis of all randomised, controlled or cohort studies, published to that time using IV ephedrine in women undergoing spinal anaesthesia for elective caesarean delivery. Five studies in 396 women were identified with total prophylactic and rescue doses of ephedrine (salt not specified) ranging from 5 mg to 47 ± 21 mg. Significant (but relatively flat) dose response relationships were noted for maternal hypertension and hypotension, and umbilical arterial pH, but there was no evidence of a dose response relationship for nausea or vomiting, fetal acidosis, or neonatal Apgar scores. The authors stated: 'The association estimated with the dose response meta-analysis was stronger for hypertension than for hypotension. These findings suggest that the use of larger doses of ephedrine (> 14 mg) does not completely eliminate hypotension but causes reactive hypertension and a minor decrease in umbilical arterial pH.'

Iqbal (2010) compared the efficacy of 10, 15, and 20 mg bolus doses of prophylactic IV ephedrine for prevention of maternal hypotension associated with spinal anaesthesia for caesarean section in 90 women. The incidence of hypotension was 53.3%, 13.3% and 3.3% and the incidence of reactive hypertension was 0, 13.3% and 46.6% in patients who received 10, 15, and 20 mg ephedrine, respectively. The incidence of nausea and vomiting was higher in patients receiving 10 mg which was attributed to hypotension. There was no difference between the groups in 1min and 5min Apgar scores. The authors concluded that 15 mg was the optimal dose of prophylactic IV ephedrine.

The sponsor stated that overall 'ephedrine when used as a pressor agent in spinal anaesthesia has a relatively flat dose response for both the risk of hypotension and risk of hypertension. Furthermore, no dose response was found in the risk of foetal acidosis or Apgar scores observed in neonates delivered from women who received a range of ephedrine doses, up to 47 mg. These results are not unexpected when the pharmacology of ephedrine is considered.' On this basis they suggested that 'a 6.3% difference in ephedrine content between the hydrochloride and sulfate formulations is unlikely to have a clinically significant impact on either the patient, assessed as risk of hypotension, risk of hypertension or nausea and vomiting, or on the foetus when used using delivery, and assessed by foetal acidosis, umbilical pH or Apgar scores.

While the data provided in this response were generated using IV ephedrine, the fact that the injection solution is a simple aqueous formulation supports a conclusion that similar results will be seem following IM or SC injection.'

Evaluation of the response:

The sponsor used 2 publications to demonstrate that there is dose response relationship for IV ephedrine used prophylactically and as rescue medication in the prevention of hypotension during spinal anaesthesia prior to caesarean delivery. It should be noted that ephedrine hydrchloride is not indicated in Europe for prophylactic treatment. The salt of ephedrine used in the 5 individual studies included in the meta-analysis was not specified in the publication, while in the second publication the ephedrine salt was stated (in a personal communication to

[12] Lee A, Ngan Kee WD, Gin T. A dose-response meta-analysis of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for elective cesarian delivery. *Anesthesia Analgesia* 2004; 98: 483-490.
[13] Iqbal MS, Ishaq M, Masood A, Khan MZ. Optimal dose of prophylactic intravenous ephedrine for spinal-induced hypotension during cesarian section. *Anaesthesia Pain & Intensive Care* 2010; 14: 71-75.

the sponsor) to be ephedrine sulfate. Most of this evidence related to doses in the range of 5 mg to 20 mg, with doses > 15 mg being more likely to cause reactive hypertension. While there was no data specifically addressing the implications of a 6.3% increase in the dose of ephedrine with ephedrine hydrochloride compared with ephedrine sulfate, it is accepted that at the doses routinely administered it is unlikely to be clinically relevant particularly as the initial dose is usually small with subsequent doses titrated based on the initial patient response. This view is supported by independent clinical expert advice obtained by the TGA. The expert stated that 'the vast majority of the use of ephedrine in anaesthesia is by intravenous titration of small boluses' and 'Much more typical practice would be to administer 3 to 6 mg boluses every 2 to 3 minutes titrated to clinical effect. Because the effective dose range is quite wide, and the drug is titrated to effect, it would be reasonable to argue that a slight variation in free available drug is not likely to be clinically important.' However the expert did comment that in certain clinical situations and patient groups, 'ephedrine doses need to be titrated carefully and in small doses, and in these setting the inadvertent administration of 'too much' drug could certainly be hazardous. Examples of such procedures would include neurovascular surgery where sudden unexpected hypertension can result in devastating intracranial haemorrhage.' The expert further indicated that this would also be important in paediatric anaesthesia.

No data was provided for IM or SC ephedrine, although the sponsor suggested that because the injection is a simple aqueous solution, then similar results could be expected. This is not considered acceptable and, as per previous comments, it is recommended that only the IV route of administration is approved.

On the basis of the data provided by the sponsor and the expert advice, the dosage and administration section of the PI will need to be revised in-line with the European SPC for ephedrine hydrochloride.

12.5. Safety question 6

There is a 6.3% increase in the dose of ephedrine with ephedrine hydrochloride compared with ephedrine sulfate. Please provide data which quantifies the implications this has for safety for each mode of administration (IV, IM, SC) and for each indication, particularly in relation to the initial dose of ephedrine administered as later doses can be titrated based on patient response. Particular attention should be paid to the effect on the foetus when ephedrine is used during labour, and to the paediatric population.

Sponsor response:

The sponsor used the same 2 publications for safety that were discussed above in response to the efficacy Question 5. As noted above, in the meta-analysis no significant dose response was observed for the incidence of nausea, vomiting, foetal acidosis, or neonatal Apgar scores. However a significant dose response relationship was noted for reactive maternal hypertension, and umbilical arterial pH. In Iqbal (2010)[13], very few neonates had Apgar scores < 7 at 1 minute or < 8 at 5 minutes, with no difference between mothers administered 10, 15, or 20 mg ephedrine.

Evaluation of the response:

As per response for Question 5.

13. Second round benefit-risk assessment

13.1. 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.

13.2. 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 6mg 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.

13.3. 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.

14. 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.

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