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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Applicant:	Flamel Ireland Limited
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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 5

1.1 INTRODUCTION 5
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 5
1.3 RECOMMENDATIONS 6

2 DRUG INFORMATION 11

2.1 DRUG 11
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS 12
2.3 DRUG FORMULATION 13
2.4 COMMENTS ON NOVEL EXCIPIENTS 13
2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN 13
2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN 17
2.7 REGULATORY BACKGROUND 17

4 PHARMACOLOGY 20

4.1 PRIMARY PHARMACOLOGY 20
4.3 SAFETY PHARMACOLOGY 24

5 PHARMACOKINETICS/ADME/TOXICOKINETICS 25

5.1 PK/ADME 25

6 GENERAL TOXICOLOGY 29

6.1 SINGLE-DOSE TOXICITY 29
6.2 REPEAT-DOSE TOXICITY 31

7 GENETIC TOXICOLOGY 31

8 CARCINOGENICITY 37

9 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY 37

10 SPECIAL TOXICOLOGY STUDIES 39

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 39

Table of Tables

Table 1. Labeling Recommendations 7
Table 2. Drug Substance Information 11
Table 3. Relevant IND Application 12
Table 4. Relevant DMFs 12
Table 5. Ingredients Employed in the Drug Product 13
Table 6. Drug Substance Impurity Information 14
Table 7. Residual Solvent Information 15
Table 8. Drug Product Specifications 15
Table 9. Summary Information on the Isomer of Ephedrine Employed in Published Nonclinical Studies Reviewed 19
Table 10. Tissue Distribution of Ephedrine and Its Metabolite Norephedrine in Dogs following Intraperitoneal Injection of L-Ephedrine (50 mg/kg) 26
Table 11. Information on The Metabolic Pathways for Ephedrine in Multiple Species 27
Table 12. Percentage of Ephedrine and Its Metabolites Recovered in Urine Obtained from Multiple Species 29
Table 13. Summary of Findings at Lethal Doses of Ephedrine in Multiple Species 29
Table 14. Summary of Findings from In Vitro Genetic Toxicology Studies in Mammalian Cells 32
Table 15. Estimated Exposure Margins for Ephedrine Doses Evaluated in Carcinogenicity Studies in Rodents Compared to the Maximum Recommended Dose for Humans Based on Body Surface Area 37

Table of Figures

Figure 1. Components of the Drug Product 13
Figure 2. Components for Proposed Container Closure System 16
Figure 3. Notable Nonclinical Advice Provided to the Applicant 17

1 Executive Summary

1.1 Introduction

Flamel Ireland Limited is seeking marketing approval for the use of ephedrine sulfate as an injectable intravenous solution for the treatment of clinically important hypotension occurring in the setting of anesthesia via the 505(b)(2) pathway. Note that the Applicant purchased Éclat Pharmaceuticals, the company that originally met with the Division on December 19, 2012 for a pre-IND meeting to discuss the development of an ephedrine sulfate drug product for marketing (see IND 116266). Flamel does not currently market this drug product and there are no FDA-approved ephedrine sulfate injection drug products to date. However, there are several marketed unapproved ephedrine sulfate injectable products. Ephedrine is listed in the Code of Federal Regulations as acceptable for over-the-counter use as a bronchodilator, topical nasal decongestant, and ophthalmic vasoconstrictor; therefore, ephedrine sulfate is not considered a new molecular entity or a new chemical entity. There is extensive clinical history of this drug substance. The Applicant is relying upon the published literature to support this application.

1.2 Brief Discussion of Nonclinical Findings

There were no original nonclinical pharmacology or toxicology studies submitted in support of this NDA application. In several meetings with the Applicant prior to submission of the NDA, the Division communicated multiple issues to the Applicant. Firstly, as ephedrine possesses two chiral centers and exists as four stereoisomers, the Applicant was directed to identify the isomer utilized in all relied upon publications for safety and efficacy of (-)-ephedrine. Secondly, it was conveyed that if there is adequate clinical experience with the drug product, no general toxicology studies would be required to support an NDA. Thirdly, if the referenced nonclinical genetic toxicology and reproductive and developmental toxicology literature do not support labeling for the drug product, these studies would be required post-approval.

The final drug product is ephedrine sulfate in water and therefore there are no novel excipients in the drug product formulation. All drug substance impurities and drug product degradants have been adequately qualified for safety. The rubber stopper is used in a marketed FDA-approved aqueous product and therefore the safety of the container closure system consisting of the glass vial and (b) (4) rubber stopper has been adequately qualified for safety.

The nonclinical findings used to support the safety of the ephedrine sulfate product are briefly discussed below. Extensive clinical experience with this drug substance and literature support the local and systemic safety of ephedrine. Published acute toxicology studies demonstrated that intravenous ephedrine caused mortality (at least 7-times the maximum recommended human dose (based on body surface area comparisons) but was generally preceded by a variety of clinical signs, including convulsions, uncoordination, and increased respiration (Chen, 1926b; Graham and

Kuizenga, 1948; Marvola, 1976; Warren and Werner, 1946). In repeat-dose toxicity studies conducted in rats and mice, ephedrine was demonstrated to decrease body weight and food consumption in the absence of treatment-related findings following dietary administration for up to 2 years. There was no evidence of test article related adverse findings in mice orally administered up to approximately 29 mg/kg (2.4-times the maximum recommended dose of 50 mg based on body surface area comparisons) and rats orally administered up to approximately 11 mg/kg (1.8-times the maximum recommended dose of 50 mg based on body surface area comparisons).

In in vitro genetic toxicology studies evaluating ephedrine, negative results were obtained in the in vitro bacterial reverse mutation assay (Ames assay), in vitro chromosome aberrations assay, or the in vitro sister-chromatid exchange (SCE) assay. However, the genotoxic potential of ephedrine sulfate has not been evaluated in an in vivo genotoxicity assay. It is recommended that an in vivo genotoxicity assay is conducted with ephedrine sulfate as a post-marketing requirement. There was no evidence of carcinogenicity at dietary doses of up to 11 mg/kg/day in rats (approximately 2-times the maximum recommended daily dose of 50 mg/day) and 29 mg/kg/day in mice (approximately 3-times the maximum recommended daily dose of 50 mg/day).

The Applicant submitted an abstract describing reproductive and developmental toxicology findings from a chicken embryo study (b) (4) . Overall, these reproductive toxicology studies were not deemed adequate to fulfill the requirements of an NDA and therefore it is recommended that ephedrine sulfate is evaluated in the standard battery of reproductive toxicology studies.

Taken together, the Applicant did not submit any new nonclinical studies to support this marketing NDA as none were required. The Applicant has provided adequate data to support the safety of the drug product substance and drug product specifications. However, several post-marketing requirements (PMRs) will be issued, which include four reproductive toxicology studies and one in vivo genetic toxicology study.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 208289 may be approved with the following PMRs and pending agreement on labeling.

1.3.2 Additional Non Clinical Recommendations

Based on the data submitted to date, the following studies are recommended as post-marketing requirements (PMRs), should this NDA be approved during this cycle:

1. Conduct a fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.

2. Conduct an embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.

3. Conduct an embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.

4. Conduct a peri- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.

5. Conduct an in vivo micronucleus assay to evaluate ephedrine sulfate.

1.3.3 Labeling

The labeling recommendations below have not been discussed with the entire review team or the Applicant. The reader is referred to the drug product labeling in the action letter for final labeling information.

Table 1. Labeling Recommendations

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
Highlights **Indication and Usage** (b) (4) for the treatment of clinically important hypotension in the setting of anesthesia.	**Highlights** **Indication and Usage** (b) (4) Alkovaz (ephedrine sulfate~~)~~ is an alpha- and beta-adrenergic agonist and norepinephrine releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.	The brand name has been updated as per the review team recommendations. The established pharmacologic class text phrase will be the first recommended for this product. The mechanism of action for ephedrine is well established in the published literature (for review see Hoffman, 2001). Liles et al. (2006) demonstrated in rats that the vasopressor effects of ephedrine are mediated via alpha-adrenergic receptors based on the attenuation of its effects in animals co-administered phentolamine, which selectively blocks alpha 1- and alpha 2- adrenergic receptors.

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Risk Summary (b) (4) in the U.S. general population is 2-4% and of miscarriage is 15-20% (b) (4)	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** Risk Summary (b) (4) There are no adequate or well-controlled studies of (b) (4) intravenous ephedrine sulfate in pregnant woman. (b) (4) Animal reproduction studies have not been conducted with ephedrine sulfate.	As per the PLLR labeling initiative, (b) (4) (b) (4)
Clinical Considerations *Fetal/Neonatal adverse*	Clinical Considerations *Fetal/Neonatal adverse*	

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
reactions (b) (4) umbilical artery pH of ≤7.2 (b) (4) Monitoring of fetal acid-base status is warranted to ensure that an episode of acidosis is acute and reversible.	*reactions* The published literature suggests that at higher total ephedrine exposures to pregnant women during birth, there is a greater frequency of cases of umbilical artery pH of ≤7.2 which is a measure of potential fetal acidosis. Monitoring of fetal acid-base status is warranted to ensure that an episode of acidosis is acute and reversible.	Defer to clinical team
(b) (4)		

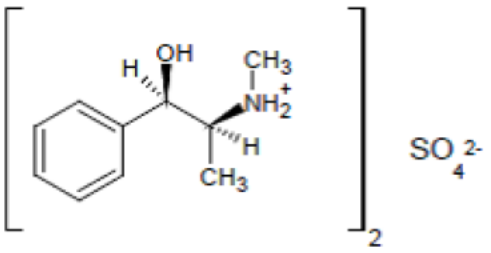
Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
11 Description [redacted] (b) (4)	**11 Description** [redacted] (b) (4)	
12 CLINICAL PHARMACOLOGY	**12 CLINICAL PHARMACOLOGY**	
12.1 Mechanism of Action Ephedrine sulfate is a sympathetic agonist [redacted] (b) (4)	**12.1 Mechanism of Action** Ephedrine sulfate is a sympathomimetic amine that acts as an agonist at α- and ß-adrenergic [redacted] (b) (4) receptors and releases norephinephrine from sympathetic neurons. Pressor effects by direct alpha and beta adrenergic receptor activation are mediated by increases in cardiac output, arterial pressure, and peripheral resistance. Indirect adrenergic stimulation arises from norepinephrine release from sympathetic nerves.	
13 NONCLINICAL TOXICOLOGY	**13 NONCLINICAL TOXICOLOGY**	
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**	
[redacted] (b) (4)	[redacted] (b) (4) Carcinogenesis: Two-year feeding studies in rats and mice conducted under the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate at doses up to	Data from the carcinogenicity study were derived from the published literature (see National Toxicology Program,1986)

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
	10 and 27 mg/kg (approximately 2- and 3-times the maximum recommended human dose of 50 mg/day on a mg/m^2 basis), respectively.	
(b) (4)	(b) (4) Mutagenesis: Ephedrine sulfate tested negative in the in vitro bacterial reverse mutation assay. (b) (4) -sister chromatid exchange and chromosome aberration assays.	These data were obtained from a published report from NTP, an organization with extensive experience conducting these types of studies (National Toxicology Program,1986).
(b) (4) have not been conducted.	(b) (4) Impairment of Fertility: Studies to evaluate the effects of ephedrine sulfate on fertility have not been conducted.	

2 Drug Information

2.1 Drug

Table 2. Drug Substance Information

Generic Name(s)	(-)-ephedrine sulfate; l-ephedrine; levo-ephedrine (1R,2S)-(-)-ephedrine
Pharmacological Class	Alpha- and beta- adrenergic receptor agonist and norepinephrine releasing agent (PROPOSED)
Structure of (-) ephedrine	
Molecular Formula	$C_{20}H_{32}N_2O_6S$

IUPAC Name	(1R,2S)-2-(methylamino)-1-phenylpropan-1-ol; sulfuric acid
Molecular Weight	428.54 g/mol
CAS Registry Number	134-72-5

2.2 Relevant INDs, NDAs, BLAs and DMFs

Ephedrine is listed in the Code of Federal Regulations as acceptable for use as an over-the-counter human drug as follows:

21 CFR Chapter	**Acceptability of Use**
§341.16	Bronchodilator Active Ingredient when used within the dosage limits established for each ingredient.
§341.20	Topical Nasal decongestant active ingredient when used within the dosage limits and dosage forms established for each ingredient.
§349.18	Ophthalmic vasoconstrictor (ephedrine hydrochloride 0.123 percent)

There are unapproved injectable products (i.e., IM, IV, and SC; 50 mg/mL) that are marketed by (b) (4). Marketing for these products appear to have started in 2004 or later.

See below for further information on relevant IND applications and DMFs.

Table 3. Relevant IND Application

Application No.	**Holder**	**Product**	**Indication**	**Status (Date)**
116266	Éclat Pharmaceuticals, LLC	Ephedrine Sulfate Injection, USP, 50 mg/mL	To counteract the hypotensive effects of (b) (4) anesthesia	Presubmission (Aug 2012)

Table 4. Relevant DMFs

Application No.	**Subject**	**Holder**	**DMF Type**	**Status**
(b) (4)			II	Active
			III	
			III	

2.3 Drug Formulation

The drug product is formulated as an injectable solution that is intended for intravenous use. See **Table 5** for excipients included in the drug product. This product is prepared in a single strength (50 mg/mL). The fill volume is (b) (4) mL in glass vials (fitted with rubber stoppers, aluminum crimp seals (see **Figure 1** for details).

Table 5. Ingredients Employed in the Drug Product

Component	Function	Total per vial	Acceptable (Yes/No)
Ephedrine Sulfate	Active Ingredient	50 mg	
Water for injection	Solvent	q.s.	**Yes**
Glacial acetic acid or sodium hydroxide ((b) (4))	pH adjustment		

The Applicant has set drug product specifications for pH of 4.5 to 7.0 and osmolality specification of 280 to 320 mOsmol/kg, which is acceptable.

Figure 1. Components of the Drug Product

Component	Function	Reference to Quality Standards	Concentration	Total/Vial
Ephedrine Sulfate, USP	Active	Certificate of Analysis	50 mg/mL	50 mg [a]
Water for injection	Solvent	USP	*q.s.*	*q.s.*
Glacial acetic acid or sodium hydroxide (b) (4)	pH adjustment	USP/NF[b]	*q.s* to pH (b) (4) if needed	*q.s* to pH (b) (4) if needed
(b) (4) clear glass vial of type 1 USP glass	Container	See specifications Section 3.2.P.7	-	Each
(b) (4) stopper	Closure	See specifications Section 3.2.P.7	-	Each
Aluminum crimp seal	Closure	See specifications Section 3.2.P.7	-	Each

USP: United States Pharmacopeia
NF: National Formulary
[a] Based on a delivery of (b) (4) per vial, actual fill with overfill i (b) (4)
[b] Both glacial acetic acid (USP) and sodium hydroxide (NF) (b) (4) USP immediately before use for pH adjustment, if needed.
-Not available

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product. See **Table 5** for the ingredients employed in the drug product.

2.5 Comments on Impurities/Degradants of Concern

The drug substance and drug product specifications for impurities conform to ICH Q3A(R2) and Q3B(R2) thresholds; therefore, there are no concerns.

Drug Substance

Table 6. Drug Substance Impurity Information

Impurity Type	Impurity	Structure	Proposed Specification (b) (4)	ICH Specification	Acceptance (Yes/No)
				NMT 0.15%	**Yes**

Table 7. Residual Solvent Information

Residual Solvent	Structure	Class	Proposed Specification (ppm)	ICH Specification (ppm)	Acceptable (Yes/No)
(b) (4)					Yes

Drug Product

Table 8. Drug Product Specifications

Impurity Type	Impurity	Structure	Proposed Specification	ICH Specification	Acceptance (Yes/No)
(b) (4)				NMT 0.5%	Yes

Container Closure System

The container closure system is composed of three components: a glass vial, (b) (4) rubber stopper, and an aluminum crimp seal (as seen in Figure 2 below). It

is noted that the very similar components have been used in Éclat's FDA-approved products neostigmine (see NDA 204078) and phenylephrine (NDA 204300).

Figure 2. Components for Proposed Container Closure System

Component	Description	Supplier
Vial	(b) (4)	
Stopper		
Crimp seal		

USP: United States Pharmacopeia

As ephedrine sulfate injection product utilizes the same stopper for Vazculep (see Sponsor's Table below) and are both aqueous solutions with overlapping pH, the safety of the container closure system is acceptable.

	Bloxiverz NDA 204078 Approval: 31 May 2013		Vazculep NDA 204300 Approval: 27 June 2014		Ephedrine Sulfate Injection, USP	
Active	Neostigmine Methylsulfate	1 mg/mL	Phenylephrine hydrochloride	10 mg/mL	Ephedrine sulfate	50 mg/mL
Microbial preservative/ antioxidant	[redacted] (b) (4)				None	-
pH buffer					None	-
pH adjustment					HCl/NaOH	Optional
Solvent					Water for injection	*qs*
pH					4.5-7.0	
Stopper					[redacted] (b) (4)	

-Not applicable

2.6 Proposed Clinical Population and Dosing Regimen

Ephedrine has been proposed for intravenous administration (bolus injections) in patients with clinically important hypotension in the setting of anesthesia. As stated in the proposed labeling, patients may be initially administered 5 to 10 mg that may be followed by additional drug as needed, not to exceed a maximum recommended human dose (MRHD) of 50 mg/60 kg (or 0.83 mg/kg). The ephedrine dose will likely be titrated to effect.

2.7 Regulatory Background

Although ephedrine is available as marketed unapproved products, there are no FDA-approved intravenous ephedrine products. The Applicant opened IND 116266 on August 21, 2012. Under this IND, the Applicant met with DAAAP for a PreIND meeting (December 19, 2012), End-of-Phase 2 meeting (November 19, 2013), and PreNDA meeting (April 23, 2015). Also, the Sponsor submitted an iPSP that was reviewed and accepted by the Division (July 13, 2015). See **Figure 3** for notable nonclinical advice provided to the Applicant (see meeting minutes from these meetings).

Figure 3. Notable Nonclinical Advice Provided to the Applicant

Date	Meeting Type	Notable Nonclinical Advice
December 19, 2012	Pre-IND	Nonclinical studies for the ephedrine drug substance should not be needed to support the a 505(b)(2) application if the published clinical

Date	Meeting Type	Notable Nonclinical Advice
		literature does not suggest any unexpected toxicity for the substance. Nevertheless, as the existing literature does not contain adequate information regarding the in vivo mutagenic potential and impact on reproductive and developmental toxicity of ephedrine, these studies may be required as post marketing requirements. Your IND must provide data to demonstrate blood compatibility and lack of adverse local tissue irritation prior to the initiation of clinical studies.
November 19, 2013	End-of-Phase 2	From the nonclinical pharmacology toxicology perspective, your proposal to qualify any drug substance impurities or drug product degradants that exceed ICH Q3A(R2), ICH Q3B(R2) qualification thresholds is appropriate. Your NDA must contain information on potential extractables and leachables from the drug container closure system unless specifically waived by the Division.
April 23, 2015	Pre-NDA	Although stopper (b) (4) appears to be made of the same rubber (b) (4) as stoppers from the FDA-approved NDAs 204078 and 204300, it is not clear from the meeting package if this stopper model is made using the same exact process and includes identical additives. If you believe that there is adequate information in the referenced DMF, include reference to the specific page number of submission dates in the DMF to support your conclusions that the extractable/leachable profiles for the rubber stoppers used under the mentioned and proposed for use here are identical[1]. We note that your drug substance specification for (b) (4) ephedrine exceeds ICH Q3A(R2) thresholds and must be adequately qualified for safety.
July 13, 2015	PSP – agreement met	Juvenile toxicology study is required to assess the impact of ephedrine on the developing central nervous system (CNS) during adolescence.

[1] The Applicant in the NDA has provided information that the stopper used in the final ephedrine drug product is the same stopper used in a previously approved FDA product and this issue has been addressed.

3 Studies Submitted

The Applicant did not submit original nonclinical studies for review. The nonclinical findings discussed below were obtained from published studies that generally appeared to employ the same isoform of ephedrine used in the drug product under review here.

Table 9. Summary Information on the Isomer of Ephedrine Employed in Published Nonclinical Studies Reviewed

Study Type	Authors	Ephedrine Isoform
Pharmacology	Liles et al. (2006)	L-Ephedrine
	Ralston et al. (1974)	Ephedrine
	Erkinaro et al. (2006)	Ephedrine
	Erkinaro et al. (2007)	
	Erkinaro et al. (2004)	
	Dullo et al. (1986)	Ephedrine HCl
	Fantoni et al. (2013)	Ephedrine
	Kasahara et al. (1985)	Ephedrine*
	Miyagoshi et al. (1986)	L-Ephedrine
	Graham and Kuizenga (1948)	Ephedrine sulfate
	Madsen et al. (1993)	Ephedrine
	Marvola (1976)	Ephedrine HCl
	Marvola and Kivirinta (1978)	Ephedrine HCl
	Meng et al. (1999)	(-)-Ephedrine
	Miller et al. (1998)	(-)-Ephedrine
	Miller et al. (1999)	(-)-Ephedrine
	Patil et al. (1965)	D(-)-Ephedrine
	Wellman et al. (1998)	(-)-Ephedrine
	Boakes et al. (1971)	(-)-Ephedrine HCl
	Ramsey et al. (1998)	Ephedrine HCl
PK/ADME	Marvola and Kivirinta (1978)	Ephedrine HCl
	Axelrod (1953)	L-Ephedrine
	Williams et al. (1973)	Ephedrine
	Marvola and Kivirinta (1978)	Ephedrine HCl
	Sinsheimer (1973)	Ephedrine metabolite
General Toxicology	Chen (1926)	Ephedrine sulfate
	Chen et al. (1926b)	Ephedrine sulfate
	Graham et al. (1948)	Ephedrine sulfate
	Marvola (1976)	Ephedrine HCl
	Warren and Werner (1946)	L-Ephedrine
Genetic Toxicology	McGregor et al. (1988)	(-)-Ephedrine
	National Toxicology Program (1986)	Ephedrine sulfate (-)-Ephedrine
	Hilliard et al. (1988)	(-)-Ephedrine
	Radakovic et al. (2011)	Ephedrine
	Storer et al. (1996)	Ephedrine sulfate
	Szybalski (1958)	Ephedrine
	Zeiger et al. (1988)	Ephedrine sulfate
Carcinogenicity	National Toxicology Program (1986)	Ephedrine sulfate (-)-Ephedrine
Reproductive Toxicology	Kinai et al. (1986)	Ephedrine
	Nishikawa et al. (1985)	L-Ephedrine
Local Toxicology	Chen (1926)	Ephedrine sulfate

*isolated from Ephedra Herbs in laboratory

4 Pharmacology

The Applicant is developing ephedrine sulfate as a therapeutic agent to increase blood pressure in settings of clinical anesthesia. Ephedrine stimulates both alpha- and beta-adrenergic receptors and indirectly enhances the release of norepinephrine from sympathetic neurons (see Hoffman, 2001), which is different than other vasopressors that act purely as $alpha_1$ adrenergic agonists, such as phenylephrine. Published findings demonstrate that ephedrine administered via various routes increases blood pressure in non-pregnant animals such as rats, dogs, and horses (Fantoni et al., 2013; Kobayashi et al., 2003; Liles et al., 2006; Madsen et al., 1993; Patil et al., 1965) and pregnant animals such as sheep (Erkinaro et al., 2006; Erkinaro et al., 2007; Erkinaro et al., 2004; Ralston et al., 1974). Ephedrine administered in animals also decreases body weight, coughing, and inflammation (Dulloo and Miller, 1986; Kasahara et al., 1985; Miller et al., 1999; Miyagoshi et al., 1986; Ramsey et al., 1998). These primary and secondary pharmacology findings are briefly discussed below.

4.1 Primary Pharmacology

Non-pregnant animals

Rats

Kobayashi et al. (2003) examined the sympathomimetic effects of l-ephedrine (70, 140 and 210 mcg/kg) and d-pseudoephedrine (210, 420, and 630 mcg/kg) in anesthetized rats. Both l-ephedrine and d-pseudoephedrine caused dose-dependent increases in blood pressure and heart rate but lower doses of l-ephedrine were required to produce comparable effects when compared to d-pseudoephedrine. Pretreatment with 6-hydroxydopamine (6-OHDA), which selectively destroys sympathetic nerve terminals, abolished the increase in mean arterial pressure and heart rate by l-ephedrine as well as d-pseudoephedrine. These results indicate that the pressor response induced by l-ephedrine is the result of norepinephrine release from sympathetic nerve terminals and that l-ephedrine is approximately 3 times more potent than d-pseudoephedrine in inducing vasopressor and tachycardiac responses in rats.

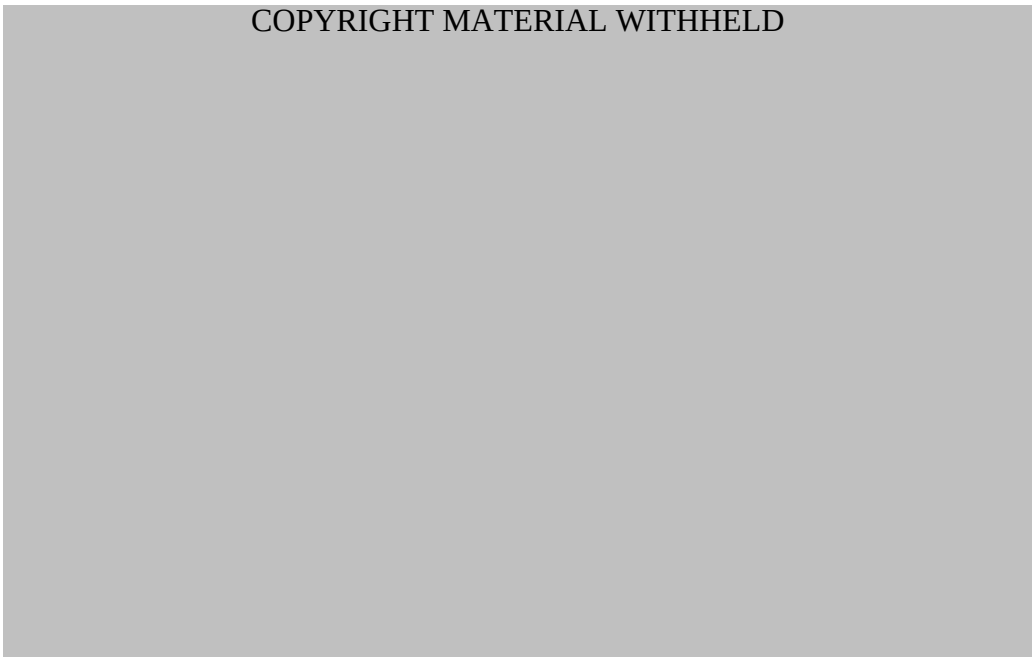
Liles et al. (2006) evaluated the mechanism by which intravenous l-ephedrine (1, 3, 10, or 30 mg/kg) altered systemic and pulmonary arterial pressure and heart rate in conscious and anesthetized male Sprague Dawley rats. The rats were prepared by catheterizing an external jugular vein for intravenous drug delivery and ephedrine was administered to rats either as a single dose or cumulative dose. The cardiovascular endpoints measured were systemic and pulmonary arterial pressure (all experiments) and heart rate (select experiments). Systemic and pulmonary pressure were increased in a dose-related manner following treatment with ephedrine (1, 3, 10, or 30 mg/kg)

under either a single dose or a cumulative-dose schedule. Also, systemic arterial pressure was increased in conscious and anesthetized rats following treatment with ephedrine at 10 mg/kg. The authors noted that the duration of the pressor effect was shorter in the conscious animals compared to the anesthetized animals. Heart rate was decreased in a statistically significant manner in the conscious rats and increased in the anesthetized rats. The authors concluded that the increased heart rate in the anesthetized animals was likely due to anesthesia induced alterations in the baroreflex function. In mechanistic studies, pretreatment with the selective $alpha_1$ and $alpha_2$-receptor antagonist phentolamine (0.5 mg/kg, IV) in conscious rats attenuated the increased systemic and pulmonary arterial pressure observed following ephedrine (10 mg/kg) alone. Pretreatment with the $beta_1$-receptor antagonist propranolol did not attenuate the pressor response observed following treatment with ephedrine (10 mg/kg) alone; however, heart rate was decreased. In regard to pretreatment with reserpine alone or co-administered with the alpha-methyl-p-tyrosine (AMPT), these catecholamine depletors did not alter the increased systemic arterial pressure observed following treatment with ephedrine. Overall, these results provided evidence that systemic and pulmonary arterial pressure responses following ephedrine treatment in rats are mediated by direct alpha-adrenergic receptor stimulation and modulated by beta-adrenergic receptors.

Dogs and Cats

Patil et al. (1965) evaluated the cardiovascular effects of intravenously administered D(-)-ephedrine, L(+)-ephedrine, L(+)-pseudoephedrine, and D(-)-pseudoephedrine in anesthetized dogs and cats. These animals were treated with atropine sulfate (1 mg/kg, IV) to avoid reflex bradycardia arising from pressor responses and monitored for changes in blood pressure and heart rate following treatment with the isomers mentioned above. Pressor effects were observed in both species following the administration of D(-)ephedrine (0.33 mg/kg), L(+)-ephedrine (0.99 mg/kg), and L(+)-pseudoephedrine (1.65 mg/kg). Depressor effects were observed in dogs (0.33 mg/kg, 3.3, 9.9, and 16.5 mg/kg) and cats (0.33, 3.3, 6.6, 13.2, and 26.4 mg/kg) following the administration of D(-)-pseudoephedrine. The magnitude and duration of this effect was increased in a dose-related manner. For example, the mean value for the blood pressure in dogs administered 3.3 mg/kg was decreased by 21 mmHg over a one-minute period, an effect that was followed by a rise in blood pressure that reportedly did not exceed 30 mmHg (duration not provided). At the highest dose tested (16.5 mg/kg), the blood pressure in dogs was decreased by 80 mmHg over an eight-minute period and there was no evidence of a secondary rise in blood pressure. In regard to heart rate, it was increased by each of the isomers tested. Heart rate was reportedly maximal at the maximum height of the pressor effect in dogs following treatment with D(-)-ephedrine, L(+)-ephedrine, and L(+)-pseudoephedrine. In regard to D(-)-pseudoephedrine, heart rate was increased in a dose-related manner. This effect peaked at 9.9 mg/kg, the penultimate dose, which suggested the saturation of the receptors that mediated this effect. Heart rate was not measured in treated cats.

Together, these data demonstrated that the pharmacological profile for D(-)-pseudoephedrine does not overlap completely with that of the other isomers evaluated.



Pregnant animals

Normal ewes

Ralston et al. (1974) evaluated the effects of intravenous ephedrine (0.25, 0.5, 1, and 2 mg/kg) in pregnant non-anesthetized ewes near term (i.e., treated between Gestational Days 132 to 142). Note that the mentioned doses were administered on the same treatment day and the subsequent dose was administered after the maternal mean arterial blood pressure and uterine blood flow returned to within 10% of control. The endpoints evaluated in pregnant ewes only included uterine blood flow, central venous pressure, cardiac output, stroke volume, and total peripheral resistance. The endpoints measured in ewes and fetus included MAP, heart rate, pH, P_{CO2}, P_{O2}, and base excess. **Statistically significant alterations were only observed in ewes, which were observed with increased values for MAP (all doses) and central venous pressure (1 and 2 mg/kg).** The highest dose that produced these effects was 2 mg/kg (human equivalent dose or HED of 1.84 to 2.33 mg/kg based on body surface area)[2]. These HEDs in pregnant sheep are approximately 2.2- to 2.8-fold higher than the maximum recommended clinical dose of ephedrine (0.83 mg/kg) based on a body surface area comparison.

Hypotensive and Hypoxemic Ewes

[2] The HED was determined, as per the FDA Start Dose Guidance assuming a 60 kg person.

Erkinaro et al. (2006) evaluated the effects of ephedrine (0.2 to 1.06 mg/kg) on maternal and fetal hemodynamic parameters in pregnant ewes in which hypotension and hypoxemia were induced. Hypoxemia was induced by increasing placental vascular resistance via a procedure that produced an embolization in this organ. Hypotension was induced in ewes 24 hours later by infusing bupivacaine 0.5% (0.3 mg/kg) epidurally over a 2-minute period. Treatment with bolus doses of ephedrine was initiated after maternal systolic arterial blood pressure dropped by ≥ 30%. The dose of ephedrine appears to have been titrated to effect. After the induction of hypotension, a variety of hemodynamic endpoints were altered. Maternal hemodynamic values were decreased in a statistically significant manner included MAP, HR, uterine blood flow (Q_{UtA}), vascular resistance (R_{UtA}), and arterial P_{CO2}. Following the termination of treatment these endpoints returned to baseline levels, except heart rate (↑). Placental hemodynamic values that were altered in a statistically significant manner following the induction of hypotension included placental vascular resistance (↑), lactate concentration (↑), arterial pH (↓) and P_{O2} (↓), and arterial base excess (↓). Following the termination of treatment these endpoints returned to baseline levels within the time frame examined, except for arterial base excess (↓) and lactate concentration (↑) which remained elevated during the recovery evaluation period examined (75 minutes). **Together, these findings provide evidence that the induction of hypotension and hypoxemia in pregnant ewes is reversed following treatment with intravenous doses (bolus injection) of ephedrine up to doses 1.06 mg/kg** (human equivalent dose or HED of 0.98 to 1.23 mg/kg based on body surface area). These HEDs in pregnant sheep are approximately 1.2- to 1.5-fold higher than the maximum recommended clinical dose of ephedrine (0.83 mg/kg) based on a body surface area comparison.

Erkinaro et al. (2007) evaluated the effects of intravenous ephedrine (0.16 to 1.17 mg/kg) on fetal endpoints measured following treatment in pregnant sheep in which hypotension and hypoxemia were induced during Gestational Days 115 to 136 (i.e., near term animals). The ewes were assigned to either a group with normal placental function or a group with increased placental vascular resistance after embolization of this organ, which results in hypoxia. Ewes were anesthetized by 0.5% bupivacaine (0.3 mg/kg), which induced hypotension. A polygraph continually recorded maternal and fetal mean arterial pressures and heart rates and umbilicoplacental volume blood flow and resistance. Lactate concentrations were measured in maternal and fetal blood samples. Doppler ultrasonography was used to record fetal cardiovascular hemodynamic endpoints. Following the induction of hypotension in pregnant ewes, statistically significant alterations were observed in P_{O2} (↓), lactate (↑), and pulsatility index values for proximal branch pulmonary artery (↑) across groups (data pooled by authors); as well as pulsatility index values for the pulmonary vein (↑) and time-velocity integral ration between the anterograde and retrograde blood flow velocity waveform components in the aortic isthmus (↓) in embolized fetuses. After treatment with ephedrine, the values for these endpoints returned to baseline levels during the recovery evaluation period examined, except for lactate concentration remained elevated over the period examined (75 minutes). **These findings provided evidence that alterations in fetal cardiovascular endpoints following the induction of**

hypotension, hypoxemia, or both in pregnant ewes are generally reversed following treatment with intravenous doses of ephedrine up to 1.17 mg/kg (human equivalent dose or HED of 1.07 to 1.36 mg/kg based on body surface area). These HEDs in pregnant sheep are approximately 1.3- to 1.6-fold higher than the maximum recommended clinical dose of ephedrine (0.83 mg/kg) based on a body surface area comparison.

4.3 Safety Pharmacology

Cardiovascular

As discussed in the primary pharmacology section of this review, the cardiovascular effects of intravenously administered ephedrine is characterized in a variety of species. See the primary pharmacology section for more details.

Graham and Kuizenga (1948) evaluated heart rate in conscious male dogs intravenously injected with ephedrine (5 mg/kg). Reductions in heart rate were observed at 13 to 63 minutes post-injection, without evidence of recovery to baseline over the period examined (data not provided or discussed).

Respiration

Graham and Kuizenga (1948) evaluated respiration rate in conscious male dogs intravenously injected with ephedrine (5 mg/kg or 100 mg/m^2). Respirations per minute appeared to be markedly increased from 36 to 63 minutes post-injection, without evidence of recovery to baseline within the period of time data were collected (data not provided or discussed). This dose is approximately 3-fold higher than the maximum dose proposed for use by the Applicant (0.83 mg/kg or 30.83 mg/m^2) when based on a body surface comparison.

Central Nervous System

The psychostimulant effects of ephedrine are well characterized based on findings from studies that evaluated alterations in locomotor activity (Marvola, 1976; Marvola and Kivirinta, 1978; Meng et al., 1999; Miller et al., 1998) and neurobiochemical markers in rodents (Wellman et al., 1998), as well as alterations in neuroelectrical activity in decerebrated cats (Boakes et al., 1971). Although these studies employed various forms of ephedrine and dose schedules, the findings demonstrated that ephedrine increased locomotor activity in rodents and that this effect occurred at doses at which increased dopamine levels were observed in the nucleus accumbens of rats. Of the studies cited above, those that evaluated intravenous ephedrine in mice are briefly summarized below (Marvola and Kivirinta, 1978; Meng et al., 1999).

Marvola and Kivirinta (1978) evaluated the excretion of ephedrine in male NMRI mice administered ephedrine (40 mg/kg) either intravenously or orally. These animals were evaluated using pharmacokinetic assessments and behavioral assessments of locomotor activity (discussed above). The dose studied increased locomotor activity in mice across the routes of administration employed. The plasma concentration of ephedrine in mice immediately after intravenous administration was 39.1 mcg/mL, which is approximately 4-fold higher than the maximum concentration following oral administration (i.e., 9.31 mcg/mL). In regard to systemic plasma concentration, the $AUC_{0-\infty}$ in mice following intravenous treatment (1072 min*mcg/mL) was slightly higher than that following oral treatment (810 min*mcg/mL). The differences in plasma levels are likely at least in part due to metabolism in the liver via the "first-pass" effect. Despite these differences in ephedrine plasma levels, the elimination half-life values measured following intravenous (26 minutes) and oral (30.6 minutes) treatment were comparable. Based on these half-life values for intravenous ephedrine it should be virtually eliminated from the plasma in approximately 2 hours following treatment; however, locomotor activity was significantly increased slightly for over 3 hours. This finding suggests that the locomotor effects may be produced, at least in part, by a metabolite of ephedrine.

Meng et al. (1999) evaluated locomotor activity in rats following intravenous administration of (-)-ephedrine[3] (0, 9.9, 19.8, 39.6, 79.2 mg/kg) in the tail vein. Photocell activity cages were employed to evaluate activity in acclimated mice. Locomotor activity was characterized based on the total number of beam interruptions over a 40-minute period. Beam interruptions appeared to be significantly increased at $\geq$ 19.8 mg/kg and peaked at 39.6 mg/kg, the top dose evaluated by Marvola and Kivirinta (1978).

Together, findings from the studies in mice demonstrated that locomotor activity was increased following the intravenous administration of ephedrine at $\geq$ 19.8 mg/kg (59.4 mg/m^2). These doses are approximately $\geq$ 2-fold higher than the maximum dose proposed for use by the Applicant (0.83 mg/kg or 30.83 mg/m^2) when based on a body surface area comparison.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The pharmacokinetics profile of ephedrine is characterized in multiple species treated via various routes. Ephedrine after intravenous administration is rapidly distributed to multiple tissues and is metabolized into several metabolites via different pathways (Axelrod, 1953; Williams, 1973; Marvola and Kivirinta, 1978). These metabolites and ephedrine are excreted via urine, which appears to be the major route of excretion

[3]The dose of ephedrine shown was originally expressed as mcmol/kg. These doses were converted to mg/kg by multiplying the molecular weight of (-)-ephedrine (165.44 g/mol or 0.165 mg/mcmol) times the dose provided by the authors (e.g., 400 mcmol/kg x 0.165 mg/mcmol = 79.2 mg/kg).

(Axelrod, 1953; Marvola and Kivirinta, 1978; Williams, 1973). Williams et al. (1973) reported that there is little fecal excretion of ephedrine across multiple animal species (species not specified). See below for a brief discussion of findings from studies that evaluated ephedrine's absorption, distribution, metabolism, and excretion.

Absorption

Marvola and Kivirinta (1978) evaluated the pharmacokinetic profile of intravenously administered ephedrine (40 mg/kg) in mice using a two-compartment open model. The mean values for plasma exposure levels were 39.1 mcg/mL for the concentration of drug immediately measured after injection (i.e., Time 0) and 1072 mcg*min/mL for $AUC_{0-\infty}$. **Overall, these data demonstrated that intravenously administered ephedrine (40 mg/kg) is rapidly absorbed following injection.**

Distribution

Axelrod (1953) evaluated the distribution of ephedrine and its metabolite norephedrine in dogs either one or two hours following intraperitoneal administration of l-ephedrine hydrochloride (50 mg/kg). Ephedrine was measured in multiple tissues at both time points mentioned (see table below). The levels of ephedrine in these tissues were markedly declined at 2 hours post treatment compared to one hour post treatment, except in fat. Norephedrine was also measured in the same tissues; however, its levels increased at 2 hours compared to those at 1 hour post-treatment. The site with the highest levels of ephedrine and norephedrine at 1 hour post-treatment was the liver and at 2 hours post treatment the kidney. **Together, these findings demonstrated that ephedrine and its metabolite norephedrine were distributed to a variety of tissues that overlapped following intraperitoneal injection of l-ephedrine (50 mg/kg) in dogs and that levels of the parent drug were significantly decreased 2 hours following its injection, whereas levels of the metabolite increased. The finding that the level of the metabolite was increased is notable given that l-norephedrine and other metabolites of ephedrine may be biologically active, based on limited findings in rodents that demonstrate the observation of increased locomotor activity at time points later than that at which the virtual elimination of ephedrine is expected (see above the Safety Pharmacology Section for a discussion of Marvola and Kivirinta, 1978).**

Table 10. Tissue Distribution of Ephedrine and Its Metabolite Norephedrine in Dogs following Intraperitoneal Injection of L-Ephedrine (50 mg/kg)

	Levels following Treatment			
	Ephedrine (mg/kg)		**Norephedrine (mg/kg)**	
Tissue	**1-Hour**	**2-Hour**	**1-Hour**	**2-Hour**
Plasma	8.6	0.9	4.6	5.7
CSF	22	4	0	4.1

Liver	**172**	25	**31**	41
Lung	85	16	21	44
Kidney	108	**28**	8.5	**77**
Brain	127	18	5.5	29
Muscle	72	8.3	5	12
Heart	68	8.3	20	15
Spleen	103	15	9.3	40
Fat	6.8	11	0	4.4

Metabolism

Studies in multiple species provide evidence that ephedrine is metabolized into metabolites that include norephedrine, hydroxyl-norephedrine, and hydroxyephedrine. The levels of metabolites formed appear to vary across species (see above for a discussion of findings from Axelrod, 1953). Of these metabolites, norephedrine is metabolized into 4-hydroxynorephedrine following intragastric administration in species that include man, rabbits, and rabbits (Sinsheimer et al., 1973). The metabolites formed following ephedrine administration are produced primarily via metabolic pathways that include aromatic hydroxylation, n-dealkylation, and deamination (Williams, 1973). Findings on the metabolism of ephedrine are briefly discussed below.

Williams et al. (1973) discussed the metabolism of ephedrine based on published studies in the following species: rats, rabbits, guinea pig, dog, and man. The three metabolic pathways that appear to be involved in the metabolism of ephedrine across these species are aromatic hydroxylation, N-dealkylation, and deamination. N-dealkylation appears to be responsible for the greatest extent of the metabolism of ephedrine across species. In rabbits, the percentage of deamination is at 91%, which is slightly larger than that for n-dealkylation. The percentage for deamination and n-dealkylation is the same in man (i.e., 10%). The low percentages for the various pathways in rats and humans is consistent with higher levels of unchanged ephedrine in urine samples collected in these species when compared to the other species mentioned (see Axelrod, 1953). **Together, this information provides insight into the metabolic pathways involved in the metabolism of ephedrine across animal species and supports findings of differences in the metabolic profile of ephedrine across species.**

Table 11. Information on the Metabolic Pathways for Ephedrine in Multiple Species

	Species – Extent of Metabolism Represented as a Percentage				
Metabolic Pathway	**Rat**	**Rabbit**	**Guinea Pig**	**Dog**	**Man**
Aromatic Hydroxylation	14	11	1	1	0
N-Dealkylation	**20**	**93**	**39**	**58**	**10**
Deamination	3	**91**	-	-	**10**

Excretion

Marvola and Kivirinta (1978) evaluated the excretion of ephedrine in male NMRI mice administered ephedrine (40 mg/kg) either intravenously or orally. These animals were evaluated using pharmacokinetic assessments and behavioral assessments of locomotor activity (discussed above). In particular, the elimination half-life for intravenously administered ephedrine was 26 minutes. Based on this value ephedrine should have been virtually eliminated from the plasma in approximately 2 hours following treatment; however, locomotor activity was significantly increased slightly for over 3 hours. This finding suggests that the locomotor effects may be produced, at least in part, by a metabolite of ephedrine.

Williams et al. (1973) discussed findings from the published literature on the excretion of unchanged ephedrine in several species that included man, dog, rabbit, guinea pig, and rat. The percentage of unchanged ephedrine excreted in urine was highest in man (61%) and rat (42%). In the other species, the percentage of unchanged ephedrine ranged from 0.5 to 6% in the other species mentioned. Note that the values discussed by the authors were comparable to findings by Axelrod (1953, see below). **Together, these findings provide evidence that suggests the percentage of unchanged ephedrine in humans and rats is comparable and much higher than that in the other species mentioned.**

Julius Axelrod (1953) evaluated the excretion of l-ephedrine and several of its metabolites in several animal species following intraperitoneal injection of 50 mg/kg of the parent drug (see the table below). The animal species employed included dogs, rabbits, guinea pigs, and rats. Although the animals were injected with 50 mg/kg, the dose levels varied across the species when expressed based on body surface area (mg/m^2, see table below). Urine levels of the parent drug and its metabolites were measured in samples obtained from these species for up to 24 hours following treatment. The proportion of the various metabolites measured is expressed as a percentage of the amount of l-ephedrine administered. The percentage of ephedrine recovered in urine samples in dogs, guinea pigs, rats, and rabbits was 6.5%, 2%, 32%, and 0.1%, respectively. Although rats were administered the lowest dose of l-ephedrine based on body surface area, this species was observed with the highest percentage of ephedrine recovered from the urine samples collected (see also Williams, 1973). In rats, the percentage of ephedrine recovered from urine samples was higher than that for any of the metabolites measured. The percentage of the norephedrine metabolite recovered from urine samples was higher than ephedrine in dogs, guinea pig, and rabbit. In rabbits, the percentage of hydroxyl-ephedrine and norephedrine combined was higher than that for ephedrine and norephedrine individually, unlike the other species. **Together, these data provided insight into the urinary excretion profile of ephedrine and its metabolites in several animal species and demonstrated that a higher percentage of unchanged ephedrine was measured in urine samples from rats compared the other species tested.**

Table 12. Percentage of Ephedrine and Its Metabolites Recovered in Urine Obtained from Multiple Species

Species	Dose (mg/kg, IP)		Percentage Recovered in Urine		
		mg/m²	Ephedrine	Norephedrine	Total Hydroxy-Ephedrine and -Norephedrine
Dog	50	1000	6.5	57.8	1.5
Guinea Pig		400	2	38.5	0.9
Rat		300	32	7.5	12.8
Rabbit		600	0.1	1.8	1.9

6 General Toxicology

6.1 Single-Dose Toxicity

Multiple published studies evaluated the toxicity profile of intravenously administered ephedrine following a single treatment (Chen, 1926a; Graham and Kuizenga, 1948; Marvola, 1976; Warren and Werner, 1946). **These studies established lethal doses levels of ephedrine in species that include rabbits (≥ 66 mg/kg), dogs (≥ 70 mg/kg), cats (≥ 75 mg/kg), and rats (≥ 135 mg/kg). Across these species, clinical signs observed following the injection of ephedrine included convulsions, incoordination, and increased respiration. These signs were also noted immediately prior to any test article-related deaths. Also, rabbits were observed with decreased blood pressure (Chen,1926b). None of these studies employed anatomic pathology evaluations.** The studies cited above are briefly discussed below.

Table 13. Summary of Findings at Lethal Doses of Ephedrine in Multiple Species Chen (1926)

Species	Lethal Dose (mg/kg)	HED (mg/kg)	Clinical Signs of Toxicity					
			Convulsion(s)	Tremor	Incoordination	Respiration Increased	Irritable to touch	Restless
Rabbit	≥ 66	≥ 21.3	X		X	X		X
Dog	≥ 70	≥ 38.9	X	X	X	X		
Cat	≥ 75	≥ 20.7*	X			X		
Rat	≥ 135	≥ 21.77	X				X	X

X = observed
* weight of cats ranged from 1.21 to 2.35 kg

Multiple sources (see references)

Species	LD_{50} (mg/kg)	HED (mg/kg)	Clinical Signs of Toxicity				
			Convulsions	Hypernea	Paralysis	Tachycardia	Agression/ Hyperkinesia
Mice	74*	6.0	X			X	X
Rats	102**	16.5	X	X	X		
Rabbits	60$	19.4					
	73**	23.5	X	X	X		

*Marvola (1976)
**Graham and Kuizenga (1948)
$Warren and Werner (1945)

Graham and Kuizenga (1948) conducted a single-dose toxicology study in rats (males only) and rabbits intravenously administered ephedrine. The endpoints reported were LD_{50} and clinical signs. The LD_{50} values established in rats and rabbits, respectively, were 102 mg/kg and 73 mg/kg. The clinical signs observed across species included convulsions, hypernea, as well as paralysis followed by prostration.

Chen (1926) evaluated ephedrine sulfate in several animal species via multiple routes of administration (see **Table** above for doses). In particular, the drug was intravenously injected via the tail vein in rats, ear vein in rabbits, external jugular, or great saphenous vein in cats, and great saphenous vein in dogs. The endpoints evaluated included clinical signs in conscious animals and respiratory and cardiovascular assessments in anesthetized animals (i.e., rabbits and dogs). The potency order (most to least) for the lethal effects of ephedrine in conscious animals was as follows: cat >rabbit ~ rat > dog (see **Table** above). Although the time of death in rats was not mentioned, death appeared to occur within 10 minutes of intravenous injection in the other species. Each species was observed with a variety of adverse clinical signs prior to death. See the **Table** above for the signs observed. Many of these signs overlapped across species. For example, all of the species exhibited convulsions. The clinical signs that were observed in a single species were tremor (dog) and irritable to touch (rat), findings that are expected at non-lethal doses across the species mentioned. In experiments in anesthetized animals (rabbits, cats, and dogs), the death of animals intravenously injected ephedrine appeared to be due to cardiac failure due to marked reductions in cardiac contractions. Also, rabbits were observed with decreased blood pressure, which appeared to be correlated with the occurrence of convulsions. The author suggested that the convulsions observed in these animals were likely due to “anemia of the central nervous system.” **These toxicities were observed in the species mentioned at doses that were ≥ 24-fold higher than the MRHD (i.e., 0.83 mg/kg) when based on a body surface area comparison**.

Warren and Werner (1945) evaluated intravenous ephedrine administration to the marginal ear vein of rabbits. Neither the injection volume nor concentration was provided. LD_{50} values were determined based on deaths that occurred up to two weeks following drug injection. Note that the animals were housed in a room maintained at 26

±1°C. Under the experimental conditions employed, the LD_{50} in rabbits was established at 60 mg/kg. There was no mention of toxicities that proceeded death in these animals.

Marvola (1976) evaluated the acute toxicity of intravenously administered ephedrine in male NMRI mice. The mice were housed five per cage and evaluated for mortality and clinical signs up to 24 hours following treatment. **The LD_{50} value for ephedrine in mice was 74 mg/kg.** Mice exhibited clinical signs that included tachycardia, hyperkinesia, piloerection, aggression, and convulsions. These toxicities were observed at an LD_{50} value (human equivalent dose of 6 mg/kg) that is approximately 7-fold higher than the MRHD (0.83 mg/kg) when based on a body surface comparison.

6.2 Repeat-Dose Toxicity

Repeat-dose toxicology studies were not required given the extensive clinical history of use for ephedrine and the proposal of an acute indication (i.e., dose titration during a single day). There are published studies that evaluated the effects of ephedrine following repeat administration via various routes (Chen, 1926b; NTP, 1986). Chen et al. (1926b) evaluated ephedrine sulfate (25 mg/day or 12.6 to 23 mg/kg) administered daily (except Sundays) in rabbits via intravenous injections of 5% (50 mg/mL) solution in the animal's ear vein for four weeks. The endpoints evaluated in these animals included local toxicity at the injection site, body weight, clinical signs, and anatomical pathology (gross pathology and histopathology). The author reported that thrombosis occurred in the veins of animals after 3 or 4 injections, especially those locally sterilized with a tincture of iodine, which was soon replaced with 70% alcohol. This effect is surprising given the lack of clinical evidence of the same finding. In regard to the other endpoints, there were no treatment-related toxicities reported. These findings suggest that doses 5- to 9-fold higher than the maximum recommended human dose of 50 mg/kg (based on HED body surface area comparison) did not produce toxicities other than thrombosis in the vein injections were made, an effect that may be due to preparation of the drug. Note that the drug is typically prepared in water when used clinically, which may explain the lack of thrombosis in veins in humans. In other repeat-dose studies conducted in rats and mice, oral ephedrine was demonstrated to decrease body weight and food consumption in the absence of treatment-related anatomical findings following dietary administration for up to 2 years (see NTP, 1986; discussed below under 8 Carcinogenicity). There was no evidence of test article related adverse findings in mice orally administered up to approximately 29 mg/kg (2.4-times the maximum recommended dose of 50 mg based on body surface area comparisons) and rats orally administered up to approximately 11 mg/kg (1.8-times the maximum recommended dose of 50 mg/60 kg individual when based on body surface area comparisons).

7 Genetic Toxicology

The potential mutagenic and DNA damaging effects of ephedrine were evaluated under various experimental conditions. Those studies that employed a negative control and

evaluated several treatment levels of ephedrine are briefly discussed below. Studies that evaluated ephedra were not reviewed below (see Yin et al., 1991). Also, a study that did not mention the treatment levels of ephedrine tested was not discussed (Szybalski, 1958). Ephedrine sulfate was negative in several in vitro studies evaluating its potential for producing mutagenicity in nonmammalian and mammalian cells (McGregor et al., 1988; NTP, 1986). However, positive findings from studies evaluating the potential for ephedrine to damage DNA in mammalian cells were reported. Chinese Hamsters Ovary (CHO) cells incubated with ephedrine were observed with slightly increased incidences of chromosome aberrations in the presence of S9 at ≥ 6400 mcg/mL and sister-chromatid exchanges (SCE's) in the absence of S9 at 1490 mcg/mL, findings deemed equivocal by the authors (NTP, 1986). **These positive findings are observed at concentrations that exceed the currently accepted top concentration recommended by the ICH S2(R1) guidance document (i.e., 1 mM or 0.5 mg/mL, whichever is lower) for mammalian cell assays (see Table 15).** Ephedrine was negative for damaging DNA in other studies (Hilliard et al., 1998; Radakovic, 2011; Storer et al., 1996). Although the findings mentioned suggest that ephedrine is not mutagenic in nonmammalian cells, there is evidence that it is genotoxic in mammalian cells at concentrations that are orders of magnitude higher than that expected in the plasma of humans that administer the maximum recommended dose. This suggests that the genotoxic levels in cells are likely not clinically relevant. See below for a brief discussion of the findings from the individual studies mentioned.

Table 14. Summary of Findings from In Vitro Genetic Toxicology Studies in Mammalian Cells

Assay	Findings	Metabolic Activity System	Concentration(s) (mcg/mL)*	Authors
Sister-Chromatid Exchange Assay	**Positive**	**No**	**1490**	NTP, 1986
	Negative	No	≤ 1250	
		Yes	8000	
Chromosome Aberration Assay	**Positive**	**Yes**	**6400 and 7000**	
	Negative	Yes	5600, 6000, 7600 and 8000	
		No	≤ 3000	
		Yes/No	≤ 4285.4**	Hilliard et al., 1998
Comet Assay		No	214.27	Radakovic et al., 2011
Alkaline Elution/Rat Hepatocyte Assay		No	≤ 4285.4**	Storer et al., 1996
Mouse Lymphoma Assay		No	≤ 450	McGregor et al. (1988)

*The ICH S2(R1) guidance recommends that the top concentration use in mammalian cell assays does not exceed 1mM or 0.5 mg/mL, whichever is lower

**This value was calculated based on the molecular weight of ephedrine (428.54 g/mol). Note that 1 mM of ephedrine equals 428.540 mcg/mL.

Mutagenesis

Ames assay

The potential mutagenic effects of ephedrine sulfate (0, 100, 333, 1000, 3333, and 10000 mcg/plate) were evaluated in *Salmonella typhimurium* strains TA100, TA1535, TA97, and TA98 in the presence and absence of S9 fractions prepared from the livers of male Sprague Dawley rats and Syrian hamsters (NTP, 1986 and Zeigler et al., 1988). There was no discussion on how the treatment levels were selected, however it is noted that the highest concentration tested exceed the maximum recommend concentration of 5 mg per plate. Also, there was no mention of using a positive control in this study. The bacterial cells were incubated with either ephedrine or solvent (DMSO) for 20 minutes at 37°C. **The test article was deemed negative for mutagenicity under the experimental conditions employed.**

Strain	Dose (µg/plate)	Revertants/plate (a,b)		
		−S9	+S9 (rat)	+S9 (hamster)

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Mouse Lymphoma Assay

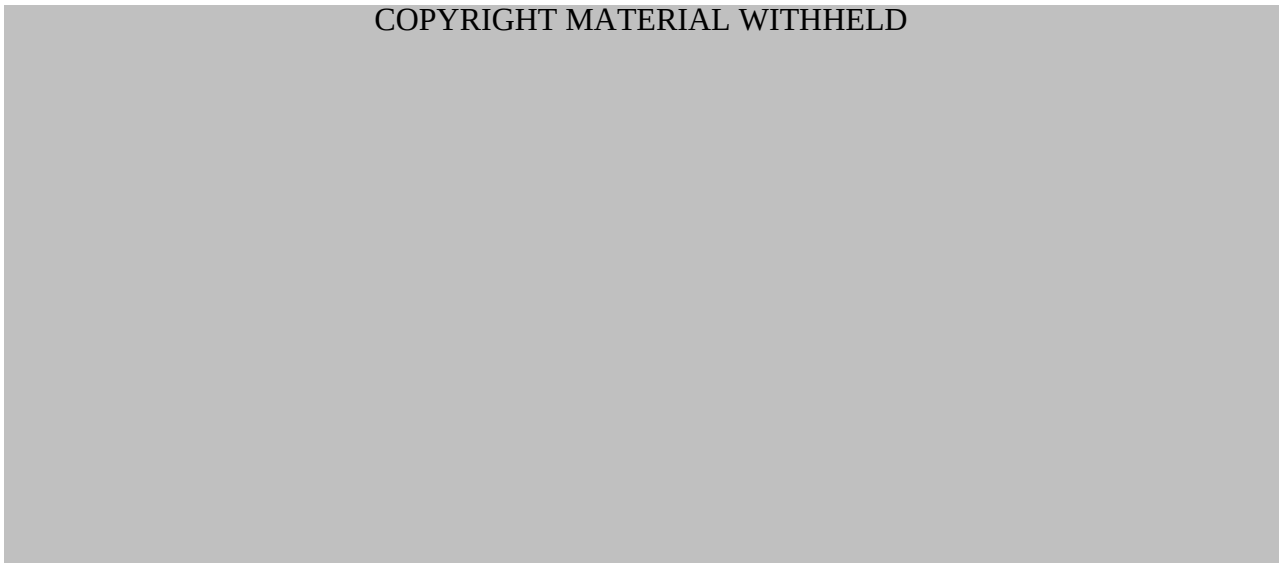
McGregor et al (1988) evaluated the potential mutagenesis of (-) ephedrine (0, 1.5, 4.5, 15, 45, 150, and 450 mcg/mL) in L5178Y mouse lymphoma cells (tk+ tk- 3.7.2.C

heterozygote). Neither a positive control nor a metabolic activation system was employed. The cells were exposed to ephedrine and incubated in tubes for 4 hours prior to being sedimented by centrifugation, washed, and re-suspended. These cell suspensions were incubated for a 2-day expression period, at the end of which the cell density was 2 x 10^5 cells/mL. The relevant endpoints evaluated were cloning efficiency, relative total growth (RTG), and mutant factor. Across the two trials conducted, RTG decreased in a dose-related manner. At the top concentration (450 mcg/mL), RTG was markedly decreased to 50% and 4%, respectively, in Trials 1 and 2 without significantly altering the mutant fraction. **These data demonstrated that ephedrine was not mutagenic up to cytotoxic doses under the experimental conditions employed (i.e., no metabolic activation system).**

DNA damage

Sister-Chromatid Exchanges (SCE's)

NTP (1986) evaluated the effects of ephedrine sulfate on sister-chromatid exchanges in Chinese hamster ovary cells in the absence (0, 100, 1250, and 1490 mcg/mL) and presence (0, 6500, 7000, and 8000 mcg/mL) of S9 fraction obtained from male Sprague Dawley rats. The cells were incubated with ephedrine for 22 to 24 hours in the absence of S9 and for 2 hours in the presence of S9 at 37°C. **A positive response was reported but was considered equivocal by NTP given that it was observed at a dose (not mentioned) at which slight toxicity of ephedrine sulfate was indicated by the necessity for delayed harvest before evaluation of cells. The positive finding presumably occurred at the highest concentration tested (1490 mcg/mL) given that the levels of SCE's at the lower doses were comparable in the absence of S9. The authors reported that the slight elevation in SCE's at the concentrations tested in the presence of S9 were not statistically significant.**



Chromosome Aberration Assay

NTP (1986) evaluated the induction of chromosomal aberrations in Chinese hamster ovary cells incubated with ephedrine sulfate in the absence (0, 1490, 1740, 1990, 2490, 2760, 3000 mcg/mL) and the presence (0, 5600, 6000, 6400, 7000, 7600, and 8000 mcg/mL) of S9 fractions obtained from male Sprague Dawley rats. The cells were incubated with ephedrine for 8 to 10 hours in the absence of S9 and for 2 hours in the presence of S9 at 37°C**. Positive responses were reported at two treatment levels (6400 and 7000 mcg/mL) in the presence of S9, a finding deemed equivocal by NTP given that these effects were observed in the mid-range of a series of extremely high doses (5600 to 8000 mcg/mL). Increases in chromosomal aberrations were not observed at the two highest doses tested. It is noted that this study was deemed not a "Valid Test" (see http://tools.niehs.nih.gov/cebs3/ntpViews/?studyNumber=002-02116-0002-0000-4).**

In another study, Hilliard et al. (1998) evaluated the potential DNA damaging effects of (-)-ephedrine sulfate (0, 6, 8, and 10 mM) in Chinese hamster ovary cells in the presence and absence of a S9-metabolic activation system. Ephedrine was dissolved in deionized water, which served as the negative control. A positive control was not employed in the study. The authors scored 200 cells per coded slide. The relevant endpoints evaluated were cell counts (% control) and percent of cells with aberrations in the presence and absence of S9. Ephedrine was tested up to the dose limit (i.e., 10 mM), at which it decreased cell count to 68% (-S9) and 83% (+S9) without producing chromosome aberrations. Precipitation was not reported in the experiments. **These findings suggested that ephedrine sulfate was negative in the chromosome aberration test up to 10 mM (or 4285 mcg/mL) in the presence and absence of S9.**

Comet Assay

Radakovic et al. (2011) evaluated the potential DNA damaging effects of ephedrine (0, 0.0005, 0.001, 0.01, 0.2, 1, 5, 50, 150, 350, and 500 mcM) in human peripheral blood

lymphocytes. This cell type was employed by the authors since most of the in vitro genetic toxicology studies on hormones were performed using human lymphocytes. The authors incubated the cells with ephedrine for 1 hour at 37°C prior to placing them on slides to solidify. These slides were placed over night in a solution in order for the cells to lyse. After lysis, the slides were placed in a buffer in the dark to allow DNA unwinding during electrophoresis over a 30-minute period. Next, the DNA was stained with ethidium bromide and analyzed with microscopy techniques to evaluate its migration into the tail of comets formed following electrophoresis. DNA damage was based on the level of migration to the tail of the comets identified. To evaluate the possible repair of DNA damage the authors treated cells with ephedrine the DNA repair inhibitors cytosine arabinoside (≤ 40 mcM) and hydroxyurea (≤ 4000 mcM). **Across the treatment conditions, there was <u>no</u> evidence that ephedrine significantly increased DNA migration in treated lymphocytes up to 500 mcM (or 214.27 mcg/mL).**

Alkaline Elution/rat hepatocyte assay

Storer et al. (1996) evaluated the effects of ephedrine sulfate (3, 7, and 10 mM) on DNA in rat hepatocytes (from male Sprague Dawley strain) following incubation over a 3-hour period. Treated cell were evaluated using cytotoxicity assays, alkaline elution assays, and pulsed-field electrophoresis assays. Cytotoxicity assays measured trypan blue exclusions, absolute cell counts, cell blebbing (light microscopy), cellular ATP content per culture (bioluminescence), and intracellular potassium levels (flame photometry). Alkaline elution assays measured the extent of DNA double-strand breaks associated with DNA degradation in dead and/or dying cells by using a spectrofluroimeter to quantify DNA that remained on the elution filter and that precipitated from fractions. Electrophoresis assays measured DNA double strand breaks 1 and 48 hours following treatment by using a densitometer or visual inspection to quantify the levels of ethidium bromide-stained DNA measured. **Ephedrine sulfate was not genotoxic up to 10 mM (or 4285 mcg/mL) given that it did not increase the alkaline elution slope at doses that appeared to be slightly cytotoxic.**

<u>Conclusions</u>

Ephedrine was not deemed genotoxic based on in vitro findings that it was neither mutagenic nor damaged DNA at relevant concentrations in the cell-based assays employed. There were instances in which positive effects were observed in the Sister-Chromatid Exchange assay (1.49 mg/mL, highest concentration) and the Chromosome Aberration assay (6.4 and 7 mg/mL, mid-range concentrations), findings that occurred at concentrations that exceeded the maximum concentration recommended by the current ICH S2(R1) guidance document (i.e., 1 mM or 0.5 mg/mL, whichever is lower). Therefore, the product labeling should include a discussion of in vitro findings that demonstrate that ephedrine was not genotoxic under conditions that were appropriate based on modern standards set by ICH and OECD guidelines (see proposed labeling above).

8 Carcinogenicity

Carcinogenicity studies were conducted in rats and mice (n=50/sex/group) fed (-)-ephedrine (0, 125, or 250 ppm/day) via their diet for up to 103 weeks (NTP, 1986). The endpoints evaluated included clinical signs, body weight food consumption, as well as macroscopic and microscopic evaluations. There was no evidence of test article-related carcinogenicity under the experimental conditions employed. Endpoints such as survival and food consumption were not altered in a test-article-related manner. In mice, body weight was decreased in a toxicologically significant manner. The estimated average amount of test article consumed per day in male mice at 125 and 250 ppm, respectively, was 14 and 29 mg/kg. The estimated averaged amount of the test article consumed per day in females at 125 and 250, respectively, was 12 mg/kg and 25 mg/kg. In rats, body weight was decreased in a toxicologically significant manner in females at Week 18 or later (≥ 125 ppm). The estimated average amount of test article consumed per day in male rats at 125 and 250 ppm, respectively, was 4 and 9 mg/kg. The estimated averaged amount of the test article consumed per day in females at 125 and 250, respectively, was 5 mg/kg and 11 mg/kg. **Together, there was no evidence of carcinogenicity in mice orally administered up to approximately 29 mg/kg (2.4-times the maximum recommended dose of 50 mg based on body surface area comparisons) and rats orally administered up to approximately 11 mg/kg (1.8-times the maximum recommended dose of 50 mg based on body surface area comparisons).**

Table 15. Estimated Exposure Margins for Ephedrine Doses Evaluated in Carcinogenicity Studies in Rodents Compared to the Maximum Recommended Dose for Humans Based on Body Surface Area

Species	Gender	Top Oral Dose (mg/kg)	HED (mg/kg)	Exposure Margin (Animal/Human*)
Rat	Male	9	1.5	1.7
	Female	11	1.8	2.1
Mouse	Male	29	2.4	2.8
	Female	25	2.0	2.4

*The human dose represented is 50 mg / 60 kg individual, which is the maximum dose recommended

9 Reproductive and Developmental Toxicology

Standard reproductive and developmental toxicology studies evaluating ephedrine were not identified in the published literature. The Applicant discussed the teratogenicity of ephedrine in rats intraperitoneally administered the drug (abstract submitted Kanai, 1986) and chick embryos topically treated (Nishikawa et al., 1985). The findings in the

chick embryos are limited given the route of administration. Findings from Kanai et al. (1986) are informative given that hazards were identified in fetuses obtained from dams with plasma levels of ephedrine of 19.2 mcg/mL (1 hour following treatment). Although these data suggest that the hazards occurred in rat fetuses at clinically relevant exposure levels, the usefulness of them are limited since the findings were not published in a peer-review journal article. See below for a brief discussion of the studies mentioned.

Kanai et al (1986) evaluated the effects of ephedrine (0.1, 1, 10, or 50 mg/kg) injected intraperitoneally (IP) in pregnant Wistar-Imamichi rats on Gestation Days (GDs) 9, 10, or 11. Fetuses were collected on GD 20 when the dams were sacrificed. In a separate group of dams, toxicokinetic assessments were made on GD 10 following the intraperitoneal injection of 50 mg/kg of ephedrine. According to the abstract, cardiovascular anomalies were observed in 20.5% of the fetuses collected. The frequency of this finding increased in a dose-related manner. The cardiovascular anomalies observed were all ventricular septal defects, two of which were associated with overriding aorta. There was reportedly no significant difference in the malformation rate among the fetuses across the GDs in which dams were treated. Extracardiac malformations were not reported in the fetuses collected. In regard to serum levels, the concentrations of ephedrine in dams were 19.2, 7.2, 1.9, and 0 mcg/mL, respectively, at 1, 3, 6, and 12 hours following the IP injection of 50 mg/kg. The concentrations of ephedrine in fetus tissue were 34.9, 9.5, 2.7, and 0 mcg/g, respectively, at 1, 3, 6, and 12 hours following treatment. **Overall, these data provide evidence that cardiovascular teratogenicity occurred in fetus across the treatment levels on either GD 9, 10, or 11 in dams. These findings in rats are informative; however, this information cannot be used for labeling purposes given that they were obtained from an abstract, rather than a peer-reviewed research article.**

Nishilawa et al (1985) evaluated cardiovascular teratogenicity and embryotoxicity endpoints in chick embryos (White Leghorn eggs) treated with L-ephedrine. L-ephedrine topically applied to eggs decreased survival and increased cardiovascular malformations in the embryonic chick in a dose-related manner. In an initial dose range finding study that topically applied l-ephedrine (0.5, 1, 5, 10, or 20 mcmol/egg) at four days of incubation, the percentage of survival for embryonic chicks was decreased in a statistically significant manner at 20 mcmol/egg. The percentage of malformations was increased in a statistically significant manner at $\geq$ 1 mcmol/egg. The malformations observed included cardiac anomalies and aortic arch anomalies. In the experiment that followed in which chick embryos (2.5 to 6 days old) were treated topically with an optimal dose (14 mcmol) selected from the previous experiment on Incubation Day 4 and returned to the incubator until Day 14, comparable incidences of aortic arch anomalies were reported. In contrast, the incidence of simple ventricular septal defects and conotruncal anomalies were markedly less in the older group (5 to 6 days) compared to the two younger groups. **Although these data provide evidence of cardiovascular teratogenicity and embryotoxicity in chick embryos following exposure to L-ephedrine, the clinical relevance of these findings is not clear.**

10 Special Toxicology Studies

Local Tolerance

The Applicant submitted findings from a study in rabbits observed with thrombosis in the vein following the administration of a 5% ephedrine sulfate solution (or 50 mg/mL) via three or four bolus intravenous injections at ≥ 16.6 mg/kg (Chen, 1926b). This concentration equals the concentration of the clinical formulation proposed for clinical use based on body surface area comparison. This nonclinical finding is likely not clinically relevant given that the finding appears to be limited to the study mentioned and not observed at the clinical doses studied in the published literature (see the Medical Officers review). Given the extensive clinical history of the marketed unapproved drug product under review here, the local tissue toxicity of the drug product can be addressed via clinical experience. Further nonclinical studies are not required.

11 Integrated Summary and Safety Evaluation

The clinical history of ephedrine is extensive. Ephedrine is an established sympathomimetic agent that stimulates both alpha- and beta-adrenergic receptors directly and indirectly enhances the release of norepinephrine from sympathetic neurons (see Hoffman, 2001). Ephedrine is known to increase blood pressure by binding to and stimulating alpha adrenergic receptors (Liles et al., 2006). Based on the long history of clinical use, nonclinical studies evaluating ephedrine were not required for approval of this NDA application. Nonclinical studies from the published literature were used to support the safety of ephedrine sulfate.

Based on findings from the published literature ephedrine is widely distributed to sites that include the liver, heart, spleen, kidney, lung, fat, cerebral spinal fluid, and brain. Ephedrine and its metabolites are excreted via urine in multiple species. Also, data from human and animal studies demonstrate the fast onset of effects and short half-life of ephedrine. For example, in single-dose toxicology studies in various animal species mortalities occurred minutes following administration of toxic doses of ephedrine. Other findings such as the alteration of blood pressure and respiration, as well as the exhibition of behaviors that include ataxia and convulsions occur soon after intravenous injection of toxic doses of ephedrine. Findings from single-dose toxicology studies provided evidence that the target sites of toxicity for ephedrine include the central nervous system, respiratory system, and cardiovascular system. Also, these toxicities were observed in animals at human equivalent doses that are approximately 7-fold or higher than the MRHD (0.83 mg/kg) based on body surface area comparisons.

In in vitro evaluations of the genotoxic potential of ephedrine, it was deemed negative in an in vitro bacterial reverse mutation assay, chromosome aberration assay, sister-chromatid exchange assay, comet assay, and alkaline elution/rat hepatocyte assay. Although positive findings were noted in some of these studies, they were evident at

high concentrations that exceed current recommendations. The Applicant was advised prior to the submission of the NDA that an in vivo genetic toxicology study would likely be required post approval given that the in vitro findings from the literature alone do not fully characterize the genotoxic potential of the drug by current standards. This requirement post approval is appropriate given the extensive clinical use of ephedrine and the acute indication sought.

In regard to reproductive and developmental toxicology, standard studies evaluating intravenous ephedrine were not identified in the published literature. The Applicant did discuss the teratogenicity of ephedrine in rats (abstract submitted Kanai, 1986) and chick embryos (Nishikawa et al., 1985). Kanai et al (1986) provided evidence that cardiovascular teratogenicity occurred in fetuses obtained from dams treated with an intraperitoneal dose of ephedrine (0.1, 1, 10, or 50 mg/kg) on either GD 9, 10, or 11. These hazards were identified in fetuses obtained from dams with plasma levels of ephedrine at 19.2 mcg/mL (1 hour following treatment). There were no findings on the plasma levels of metabolites for ephedrine, which may be at least in part be responsible for the toxicities demonstrated. These findings in rats are informative; however, this information cannot be used for labeling purposes given that they were obtained from an abstract, rather than a peer-reviewed research article. Studies reported in abstract only form may not have been able to be repeated and are not peer-reviewed. Interestingly, evidence of cardiovascular teratogenicity was also observed in chick embryos following topically exposure of eggs to L-ephedrine (= 6 mcg/mL, see Nishikawa et al., 1985). These authors reported these findings and embryotoxicity (8.57 mcg/mL) following topical exposure through the egg shell. As definitive studies were not identified in the literature and the literature references available suggest adverse effects with unclear clinical significance, the full battery of reproductive and developmental toxicology studies must be completed for this drug product. These studies will be required post approval given the extensive clinical experience of ephedrine. The design of the definitive GLP reproductive and developmental toxicology studies should be discussed with the Applicant. Ideally, they should mimic the clinical use of the drug in order to dissociate, if possible, any direct effects of the drug from the indirect pharmacodynamics effects of the drug on the cardiovascular system.

Based on the information provided to date, from a nonclinical pharmacology toxicology perspective, NDA 208609 may be approved with post-marketing requirements and pending agreement on drug product labeling.

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/s/

NEWTON H WOO on behalf of MARCUS S DELATTE
04/04/2016

NEWTON H WOO
04/04/2016

RICHARD D MELLON
04/04/2016
I concur that NDA 208289 may be approved from the nonclinical pharmacology toxicology perspective and with the recommended PMRs and labeling changes.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208289 **Applicant:** Éclat Pharmaceuticals **Stamp Date:** June 30, 2015

Drug Name: Ephedrine Sulfate Injection, USP **NDA Type: 505(b)(2)**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		No new nonclinical studies were required for this NDA. All nonclinical literature references required to support the b2 application were submitted. The submitted acute toxicology studies appear to be the only toxicology studies in which ephedrine was intravenously administered. The Sponsor did not identify published findings from fertility, prenatal and postnatal development, and local tolerance studies; however, this was not deemed a filing issue.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		X	Not applicable. See above.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?		X	Not applicable. See above.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?		X	Not applicable. No new nonclinical studies were required for this NDA.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		The Sponsor proposed specifications that appear to be consistent with ICH standards. To support the safety of the rubber stopper proposed for use, extractable/leachable data were submitted to this b2 application.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	-	-	This parameter is not applicable to the application under review.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		The Sponsor provided a rationale to support the reliance to the nonclinical literature.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no potential review issues that need to be forwarded to the Applicant at this time.

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