LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Efedrin Unimedic
(ephedrine hydrochloride)

SE/H/1679/01/DC

This module reflects the scientific discussion for the approval of Efedrin Unimedic. The procedure was finalised on 2018-03-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Unimedic Pharma AB has applied for a marketing authorisation for Efedrin Unimedic, 5 mg/ml, solution for injection. The active substance is ephedrine hydrochloride. Ephedrine is a sympathomimetic with direct and indirect effects on adrenergic receptors. It has α- and β-adrenergic activity and has pronounced stimulating effects on the central nervous system. The main effects of therapeutic doses of ephedrine are relaxation of the smooth muscle of the bronchial tree, and when norepinephrine stores are not depleted, cardiac stimulation and increased systolic and usually increased diastolic blood pressure. The use of Ephedrine IV for the management of hypotension during spinal, epidural and general anaesthesia is well established in the clinical practice.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

No new animal or in vitro studies have been performed with Efedrin Unimedic. This is acceptable since the use of ephedrine is well established in the clinic. A non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology based on published scientific literature has been provided and is considered to be adequate.

Efedrin Unimedic 5 mg/mL is intended to be used as an alternative to currently available treatment on the market and the environmental exposure to the drug substance is not expected to increase significantly. An environmental risk assessment is therefore not considered to be needed.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The pharmacokinetic documentation consists solely of bibliographic data. The product is considered representative of the products as investigated in the literature containing well-known excipients and administered as an intravenous injection.

Absorption
As follows an intravenous injection, all ephedrine is available systemically.

Distribution
Protein binding or volume of distribution following IV administration of (-)-ephedrine are unavailable.

Elimination
Excretion
The data is limited but indicates that approximately 70-80% of ephedrine is excreted unchanged in urine. Hence renal elimination is the main elimination pathway. Ephedrine is also metabolised to some extent. The elimination depends on urine pH with increased elimination of ephedrine with increasing pH of urine.

Metabolism
The data is limited but indicates that ephedrine is metabolised to some extent mainly by N-demethylation to norephedrine and to a lesser extent by oxidative deamination to benzoic acid and 1,2-dihydroxy-1-phenylpropane.

Special populations
There are no available data. Given that renal elimination is the main elimination pathway, the elimination may be decreased in patients with impaired renal function. The effect of hepatic impairment of ephedrine elimination is expected to be low.

Interactions
The only reported pharmacokinetic interaction for ephedrine is with dexamethasone. Ephedrine has been reported to increase the clearance of dexamethasone.

IV.2 Pharmacodynamics

Ephedrine is a sympathomimetic amine with a direct effect on alpha and beta receptors and an indirect effect by increasing the release of norepinephrine in the sympathetic nerve endings. Like all sympathomimetic agents ephedrine stimulates the central nevous system, the cardiovascular system, the respiratory system and the sfincters of the gastrointestinal and urinary systems. The β-adrenergic effects are mediated via stimulation of the cyclic adenosine 3',5'-monophosphate (cAMP), through the enzyme adenyl cyclase. The α-adrenergic effects are mediated through inhibition of adenyl cyclase.

The indirect effect consists of the release of norepinephrine from the sympathetic nerve endings. If long-term dosing of ephedrine takes place, the norepinephrine stores may be depleted that can result in tachyphylaxis.

The pharmacodynamics documentation consists solely of bibliographic data. The primary pharmacodynamic actions of ephedrine have been studied in a number of small clinical studies and ephedrine increase MAP and ventricular contractility and restore CO. The data thus support the use of ephedrine in hypotension associated with anaesthesia.

The study data is limited, but there are well known responses to ephedrines' actions for example relaxation of the smooth muscle of the gastrointestinal tract, effect on urogenital system, central nervous system and eye pupil. Most of this information has adequately reflected in the SmPC.

The concomitant use of ephedrine and other sympathomimetics, halogenated volatile anaesthetics, MAO-a inhibitors and other well documented know interactions have been adequately discussed and the SmPC has been amended with warnings.

IV.3 Clinical efficacy

More than 20 publications are submitted to support the efficacy of ephedrine. In the studies different approaches have been used; either ephedrine has been given at a fixed time point shortly after the induction of anaesthesia or as bolus doses at the first sign of hypotension.

The majority of studies are of acceptable standard and most of them were randomised. A large number of clinical studies, especially concerning the use of ephedrine for prevention of hypotension are available. In contrast, bibliographical data supporting the treatment of hypotension is less robust. Due to differences in the definitions of hypotension, decisive conclusions and the comparisons across studies are difficult to make. The totality of data, however, consistently shows a convincing effect of ephedrine in the management of hypotension associated with spinal and epidural anaesthesia.

In general, published studies support Efedrin 5 mg/ml solution for injection for the treatment and prevention of hypotension in the general, spinal and epidural anaesthesia.

IV.4 Clinical safety

In general, ephedrine is administered in a clinical setting with high controlled surveillance activities. Its clinical use is well-established.

The Applicant has provided an adequate overview of the safety profile of ephedrine. Some of the adverse reactions are only supported by reference literature. This is acceptable considering the vast experience of ephedrine use. The adverse reactions and well established safety profile are generally adequately reflected in the proposed SmPC.

IV.5 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Efedrin Unimedic.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed in RMP

Safety specification
Summary table of safety concerns as approved in RMP

Important identified risks	Arrhythmia
Important potential risks	Arterial hypertension
Missing information	Use in children below 1 year of age Effects on fertility and pregnancy

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report for content making reference to Efedrin

Stragen 3 mg/ml SE/H/1055/01/DC and for layout making reference to Fenylefrin Unimedic SE/H/1551/01-02/MR.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Efedrin Unimedic 5 mg/ml solution for injection is proposed for the treatment and prevention of hypotension in the general, spinal and epidural anaesthesia. The efficacy studies discussed were restricted to the indication applied for and to IV use of ephedrine. More than 20 publications are submitted to support the efficacy of ephedrine for the proposed indication. In the studies different approaches have been used; either ephedrine has been given at a fixed time point shortly after the induction of anaesthesia or as bolus doses at the first sign of hypotension.

Clinical trials in the publications submitted to support the efficacy of Efedrin Unimedic demonstrated ephedrine's ability to increase blood pressure. The majority of studies are of acceptable standard and most of them were randomized. Most of the subjects in the clinical trials in the submitted publications who received ephedrine were female undergoing spinal anesthesia for caesarean section. Although the differences in the definitions of hypotension, study design and outcome across studies published are observed, the totality of data, however, consistently shows a convincing effect of ephedrine in the management of hypotension associated with spinal and epidural anaesthesia.

The Applicant has also provided an adequate overview of the safety profile of ephedrine. The adverse reactions are generally adequately reflected in the proposed SmPC.

No safety issues identified in the review of this application require post-market risk evaluation and mitigation strategies.

The quality of the generic product, Efedrin Unimedic, is found adequate. There are no objections to approval of Efedrin Unimedic, from a non-clinical and clinical point of view. The product information is acceptable.

The benefit/risk ratio is considered positive and Efedrin Unimedic, 5 mg/ml, solution for injection is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Efedrin Unimedic, 5 mg/ml, solution for injection was positively finalised on 2018-03-22.

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MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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