LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Efedrin Stragen
(ephedrine hydrochloride)

SE/H/1055/01/DC

This module reflects the scientific discussion for the approval of Efedrin Stragen. The procedure was finalised on 12 October 2011. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Stragen Nordic A/S has applied for a marketing authorisation for Efedrin Stragen solution for injection, pre-filled syringe 3 mg/ml. The active substance is ephedrine hydrochloride. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Efedrin Stragen is presented in the form of Solution for injection, pre-filled syringe containing 3 mg/ml of ephedrine hydrochloride. The excipients are controlled to the corresponding monograph of the Ph. Eur. Efedrin Stragen 3 mg/ml, solution for injection is filled in syringe.

II.2 Drug Substance

Ephedrine hydrochloride is a white or almost white, crystalline powder or colourless crystals. It is very soluble in water and freely soluble in alcohol.
Ephedrine hydrochloride is described in the Ph. Eur. and subject of the Certificate of suitability.

Stability studies have been conducted and the data provided are sufficient to confirm the retest period as mentioned in CEP.

II.3 Medicinal Product

Efedrin Stragen 3 mg/ml solution for injection, pre-filled syringe is formulated using excipients described in the current Ph Eur. No excipients of human and animal origin is used.

The product development has taken into consideration the physico-chemical characteristics of the active substance and product, such as solubility, pH, osmolality, particulate contamination.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, without any special temperature storage conditions and with the statement “Store the blister in the outer carton, protect from light”.

III. NON-CLINICAL ASPECTS

Ephedrine is a well known sympathemimetic amine and relevant preclinical information about it has been presented using published scientific literature. No additional preclinical studies or

clinical trials have been conducted. This is acceptable since comprehensive information exists on its pharmacology of ephedrine. For a summary of pharmacological properties of ephedrine, please see summary under clinical pharmacodynamics.

The acute toxicity of ephedrine is studied in mice, rat, rabbits and guinea pigs using different routes of administrations. At toxic dose levels, ephedrine caused mainly clinical signs of toxic effects on the central nervous system such as hyperkinesia, convulsive seizures, ataxia, lethargy, and epistaxis.

A limited number of repeated dose toxicity and carcinogenicity studies have also been conducted in mice and rats with drug administration either in drinking water or in the diet. Reduction of bodyweights and partly food consumption and angiectasis of the adrenal gland and pheochromocytomas has been shown in repeated dose toxicity and long-term carcinogenicity studies respectively. No carcinogenic effects has been shown in these studies. Although there are some uncertainties with these studies, including systemic exposure data, these long term carcinogenicity studies are useful, and outweigh the absence of in-vivo genotoxicity studies.

Albeit, ephedrine is a secondary amine that might be N-nitrosated after oral intake, leading to conversion to N-nitrosoephedrine, a compound which has been reported to be carcinogenic in animals. To which extent ephedrine converts to this secondary amine upon iv administration of ephedrine is not addressed, but it is considered an acceptable uncertainty for the intended use of this product.

Genotoxicity has been studied in vitro studies, which some of them showed some equivocal effects. In-vivo genotoxicity testing is lacking. This can be accepted given that there are two carcinogenicity studies available with ephedrine.

The possible teratogenicity of ephedrine is broadly discussed in the literature, but only investigations in hens eggs are available and no teratogenicity study in rats or rabbits according to currently valid guidelines. Effects on reproduction are therefore not sufficiently tested in preclinical studies. However, the concerns raised in the clinic are the effects of ephedrine on the foetal heart rate and development of fetal acidosis in cases when ephedrine are administered either for hypotension during epidural anaesthesia or during caesarean section which are well recognized in the clinic and are adequately addressed in the SPC.

No studies on possible local effects of ephedrine are available. The clinical experience dose not raise any concern about the local tolerance effects of ephedrine given by intravenous rout of administration.

The approval of Efedrin Stragen in Europe will not result in a significant increase of the total quantity of the active substance of Efedrin Stragen released into the environment and no environmental risk assessment (ERA) is needed.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ephedrine is a well known sympathomimetic. No original data was submitted but the clinical aspects were supported by a recent and adequate review of the literature concerning all the relevant clinical aspects.

IV.2 Pharmacokinetics

Literature data on pharmacokinetics of ephedrine seems to be sparse according to the application. The pharmacokinetic data are primarily based on orally administered ephedrine with only one study administering ephedrine intravenously. The measured parameter was in all studies urine excretion of ephedrine and in some cases metabolites. Many of the studies referred to in the application were performed in the sixties and seventies and included a very low number of subjects, 1-3 subjects, and consequently the statistical analysis of data are not fully in line with the standard methods used today.

Although data are limited they indicate that ephedrine is eliminated primarily by renal excretion of parent drug and metabolites, most of the drug is excreted unchanged. A small study with three subjects reports that 27% (range 15-38%) of the ephedrine dose was excreted as metabolites 24 hours after oral dosing. The elimination half-life of ephedrine is dependent on urinary pH, with shorter half-life for acidic urine.

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

IV.3 Pharmacodynamics

A brief description of the mechanism of action has been provided, however, not supported by original publications. This is acceptable considering that ephedrine is a well known substance.

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 (CNS). It is believed that β-adrenergic effects result from stimulation of the production of cyclic adenosine 3',5'-monophosphate (cAMP) by activation of the enzyme adenyl cylase, whereas α-adrenergic effects result from inhibition of adenyl cyclase activity. Ephedrine also has an indirect effect by releasing norepinephrine from its storage sites. With prolonged use or if doses are given frequently, ephedrine may deplete norepinephrine stores in sympathetic nerve endings and tachyphylaxis may develop to the cardiac and pressure effects. 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. Responses to ephedrines' actions also include relaxation of the smooth muscle of the gastrointestinal tract, the urinary bladder and dilation of the pupils.

The primary pharmacodynamic actions of ephedrine have been studied in a number of small clinical studies. The data support that ephedrine increase MAP and ventricular contractility and restore CO. The data thus support the use of ephedrine in hypotension associated with anaesthesia. A small study also evaluated the effect of ephedrine on QT and T-wave changes. Although the study does not meet the standards of a thorough QT-study, the doses given were reasonably high as compared to the currently recommended doses. No changes in QT or T-waves were observed. Since ephedrine is often used in obstetric surgery, i.e. ceasarian section, studies concerning the effects of ephedrine on foetal ANP, circulation and acidosis have also been reviewed. An increase in foetal ANP was observed, however no difference was observed when compared to phenylephrine. Ephedrine had no effect on foetal renal artery circulation but the use of ephedrine is associated with a higher risk of foetal acidosis. This is further discussed in the safety section of this report.

Secondary pharmacodynamic effects of ephedrine have also been reviewed. These effects are well known and the information is adequately reflected in the SPC.

The pharmacodynamic interactions with other drugs have also been reviewed. Adequate warnings, especially regarding concomittant use with other sympathomimetics as well as halogenated volatile anaesthetics, are included in the SPC.

IV.4 Clinical efficacy

Hypotension is a significant complication in anaesthesia both in adults and children. In obstetric surgery, hypotension may jeopardise the placental circulation with the risk of foetal acidosis.

The efficacy studies discussed were restricted to the indication applied for (i.e., hypotension, especially with spinal, epidural or general anaesthesia) and to IV use of ephedrine. In the studies different approaches have been use; 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. As hypotension, especially in spinal anaesthesia, occurs rapidly after induction this stratification it may be discussed whether such stratification is clinically meaningful. In this assessment no stratification has been made with regards to the timing of the dose.

No formal dose finding studies were provided. A variety of different dosing regimens have been used in the cited publications. The wording of the posology is taken from product monographs. However, the totality of the presented clinical data supports the recommendation to give 3-6 mg (9mg) ephedrine as repeated injections depending on the patient's response, considering that the patient is continuously monitored. Larger bolus doses appear to be associated with a higher risk of hypertension, thus the strategy to give smaller doses repeatedly until sufficient blood pressure response is achieved is supported. The dose recommended for children is in line with the BNF for children and further supported by the data by Tagushi and is considered acceptable.

A recommendation to reconsider the choice of treatment after 30 mg is given. There is no available data in support of the proposed maximal dose of 150 mg/24 hours. This dose is, however, widely recommended for other registered ephedrine products and is therefore acceptable.

A large number of clinical studies, especially concerning the use of ephedrine in obstetric surgery are available. The majority of studies are of acceptable standard and most of them were randomised. Due to differences in the definitions of hypotension, comparisons across studies should be made with caution. 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 anaesthesia, the number of studies is lower and the results less robust but the data is still considered sufficient to support the indication. Ephedrine has been shown to restore hypotension induced by anaesthesia. Bradycardia appears to be less common with ephedrine when compared to phenylephrine which correlates with maintained cardiac output. This could be confirmed in some of the studies.

In addition to the studies relevant to the applied indication and posology, the ten studies investigating the effect of ephedrine infusion compared to other vasopressors in the treatment and prevention of hypotension in caesarean section were provided. Also when administered as an infusion, ephedrine was found efficient in maintaining blood pressure.

IV.5 Clinical safety

An adequate overview of the safety profile of ephedrine was provided. Some of the adverse reactions are only supported by reference literature and monographs. This is acceptable considering the vast experience of ephedrine use. The adverse reactions are adequately reflected in the SPC.

In addition, some of the adverse reactions have been discussed in more detail. Higher doses of ephedrine are associated with a risk of hypertension. This is to be expected due to the mechanism of action. This is also true with regards to the risk of cardiac events such as coronary vasospasm that may lead to myocardial infarction. Since hypertension is associated with higher doses, the dosing regimen proposed where relatively low doses are given repeatedly depending on the patient's response is endorsed.

Further safety data on the effects on the foetus has also been provided. It is concluded that although ephedrine use in the management of hypotension caused by spinal anaesthesia may increase the risk of foetal acidosis this does not appear to be reflected in a worse outcome in for instance Apgar score.

No original safety data concerning special populations has been provided. No data on the safety in children is publicly available. The safety profile in children is not expected to be different from that in adults. As ephedrine firstly is used in situations where the patient is under strict monitoring and secondly ephedrine is titrated according to clinical response, no special precautions are considered necessary when treating elderly patients with (potential) cardiovascular disease and/or renal impairment.

Adequate warnings regarding concomitant diseases are included in the SPC.

IV.6 Discussion on the clinical aspects

Ephedrine is a well known, sympathomimetic with direct and indirect effects on adrenergic receptors. Sufficient, albeit limited, data on the pharmacokinetics of ephedrine has been presented.

The use of ephedrine in the treatment of hypotension associated with general, spinal and epidural anaesthesia is supported by the submitted data.

The safety profile of ephedrine is well known and the adverse reactions are considered possible to handle taking into account that ephedrine is used in situations where the patient is under strict monitoring.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Portuguese.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Efedrin Stragen is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Efedrin Stragen was successfully finalised on 12 October 2011.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se