LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Tetraspan 60 mg/ml
Tetraspan 100 mg/ml

(Hydroxyethyl starch 130/0.4, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium acetate, malic acid)

SE/H/609/01-02/MR

This module reflects the scientific discussion for the approval of Tetraspan. The procedure was finalised at 28 September 2006. 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

B. Braun Melsungen AG has gained approval for a marketing authorisation for Tetraspan, a solution for infusion containing the active substance hydroxyethylated starch (60 or 100 mg HES 130/0.42 per ml) and the electrolytes sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium acetate and malic acid. The electrolyte ions are judged to contribute to the clinical efficacy and are therefore considered as active substances.

The product is indicated for *"treatment of imminent or manifest hypovolaemia and shock."*

II. QUALITY ASPECTS

II.1 Introduction

Tetraspan is presented in the form of solution for infusions containing 60 or 100 mg/ml of hydroxyethyl starch with a molecular mass of 130,000 and a molar substitution of 0.42. The electrolytes sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium acetate and malic acid are regarded as active substances and the excipients are water for injections used as solvent and sodium hydroxide used as pH adjuster. The solutions are filled in two different containers, a container/bottle of polyethylene (Ecoflac plus) or a plastic bag (Ecobag).

II.2 Drug Substance

Hydroxyethyl starch does not have a monograph in the Ph Eur. Information on *hydroxyethyl starch*, obtained from potato starch by hydroxyethylation and hydrolysis, has been provided in the dossier.

Malic acid does not have a monograph in the Ph Eur but is controlled according to its monograph in the German pharmacopoeia (DAB). Sodium chloride, potassium chloride, calcium chloride, magnesium chloride and sodium acetate all complies with the requirements in their respective Ph Eur monographs.

Hydroxyethyl starch is a fine white tasteless and odourless powder, freely soluble in water and practically insoluble in ethanol and ether. The structure of hydroxyethyl starch has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

All drug substance specifications include relevant tests and limits and the analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted for hydroxyethyl starch and the data provided are sufficient to confirm the retest period. For the electrolytes, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium acetate trihydrate and malic acid no investigations on stability have been carried out. These drug substances are tested prior to use on conformity to specifications.

II.3 Medicinal Product

Tetraspan 60 mg/ml and 100 mg/ml, solution for infusion are formulated using excipients described in the current Ph Eur.

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 restrictions in storage temperature.

Compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) has been declared by the company. No material used in the manufacturing originates from animal species susceptible to TSE.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

The applicant has submitted published data covering the main conventional toxicity areas for the short-treatment with HES-containing products, i.e. general toxicity (up to 3 months in rabbit), reproduction toxicity (segment II in mice, rats and rabbits) and genotoxicity (Ames test). Potentially negative effects from tissue accumulation HES was also addressed.

Taken together, observed undue effects may arise from both systemic distributed HES (e.g. bleeding and anaphylactic reactions) and tissue accumulated (reversible histological changes associated with clinical adverse events such as worsening of hepatic dysfunction (liver) and the appearance of pruritus (skin/storage in cutaneous nerves). The extent of histopathological events would be dependent on duration of treatment and cumulative dose of HES and the initial size of the administered HES-molecule. It appears thus advantageous to keep the amount of organ-accumulated HES as low as possible. In this respect, Tetraspan together with Venofundin, InfuHesalin 130 and Voluven are the preferable expanders among the HES-containing products.

Submitted reproduction toxicity data showed several alterations upon significant hypervolemic HES-treatment during pregnancy in animals. The fetal abnormalities (mouse and rabbit) are considered by the applicant to be the result of marked hemodilution and subsequent hypoxia during the susceptible period of gestation. The less pronounced effects with the electrolyte solutions (Ringer and saline) is considered to be due to a relatively lesser hypoxia as they diffuse much faster from the circulation. The rat findings (vaginal bleeding and associated miscarriages) could partly be explained by direct effects of circulated HES on the blood coagulation (i.e. specific depression in plasma Factor VIII level and negative effects on platelet number and function) above simple haemodilution. The findings in rat are given in the SPC. The proposed text in SPC section 4.6 is considered adequate regarding the information from animal reproductive toxicity studies and the clinical recommendation.

In conclusion, the presented preclinical data do not suggest any special concern for humans because of the novel electrolyte composition in Tetraspan. The submitted published toxicity data are considered sufficient to recommend Tetraspan for marketing approval from a preclinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

The pharmacokinetic documentation contained bibliographic data regarding the distribution, metabolism and elimination of HES and also two pharmacokinetic studies performed by the applicant as well as one bioequivalence study.

The application contains an adequate review of published pharmacokinetic data for HES.

Bioequivalence study

One bioequivalence study was performed at AAI Deutschland GmbH & Co KG, Neu-Ulm, Germany in October-December 2002. The study aimed at establishing bioequivalence between 6% HES 130/0.4 in ion adapted solution produced by Braun Melsungen AG (Tetraspan 6%) and Venofundin (6% HES 130/0.4 in 0.9% saline solution produced by Braun Melsungen AG). The study was a randomised, double-blind, single-dose two-way cross-over study. Twenty healthy male volunteers (age 18-45 years) were included in the study. All subjects completed the study.

Results

Table 1. Pharmacokinetics of HES after single dose administration.

		Test (6% HES 130/0.4 in ion adapted solution = Tetraspan 6%)		**Reference (6% HES 130/0.4 in 0.9% saline solution = Venofundin 6%)**	
Parameter	**Unit**	**geom. mean**	**geom. %CV**	**geom. mean**	**geom. %CV**
AUC_{0-12}	mg/ml*h	39.65	15.4	38.44	16.2
$AUC_{0-\infty}$	mg/ml*h	44.55	16.3	43.0	16.5
C_{max}	mg/ml	11.3	15.1	11.0	13.1
$t_{1/2}$	h	4.17	11.2	4.04	13.5
CL	ml/min	19.1	14.7	19.7	15.4
V_z	l	6.89	17.7	6.89	22.3

The calculated point estimates and the corresponding 90% confidence intervals of the test/reference ratios for AUC_{0-12}, $AUC_{0-\infty}$, C_{max} and $t_{1/2}$ are given below.

Parameter	Ratio Test / Reference	
	Estimate	90% confidence interval
AUC_{0-12}	103.17%	(101% , 105%)
$AUC_{0-\infty}$	103.64%	(102% , 105%)
C_{max}	102.21%	(98% , 106%)
$t_{1/2}$	102.32%	(97% , 110%)

The 90% confidence intervals for AUC_{0-12}, $AUC_{0-\infty}$, C_{max} and $t_{1/2}$, were within the predefined bioequivalence acceptance range of 80%-125% (CPMP/EWP/QWP/1401/98). Bioequivalence has been established between Tetraspan 6% and Venofundin 6%.

IV.3 Discussion on the clinical aspects

The application contains an adequate review of published pharmacokinetic data for HES. Data obtained in a pivotal study performed by the applicant demonstrate that Tetraspan is pharmacokinetically bioequivalent to the approved product Venofundin that contains HES in 0.9% saline solution.

As bioequivalence was demonstrated between Tetraspan and Venofundin, the pharmacokinetic documentation for Tetraspan could be used to bridge to efficacy and safety data for Venofundin.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The risk/benefit ratio is considered positive and Tetraspan, 60 and 100 mg/ml, solution for infusion is recommended for approval.

In connection with the MRP approval the applicant prepared a list of post-approval commitments and will fulfil the requirements of the new Guideline on Plastic Immediate Packaging Materials within three years.

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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
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Internet: www.mpa.se E-mail: registrator@mpa.se