LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sabumalin / Sanohex / Sabufarm

100 µg/dose, pressurised inhalation, suspension
(Salbutamol sulphate)
SE/H/603/01/DC, SE/H/601/001/DC, SE/H/602/001/DC

EMEA/H/A-29/990
EMEA/H/A-29/991

Applicant: HEXAL AG

This module reflects the scientific discussion for the approval of Sabumalin, Sabuhex and Sabufarm. The DC procedures for Sabumalin and Sabuhex were referred to the CMDh 2007-12-20 and after CMDh discussions and CHMP referrals, positive Commission Decisions were issued by the European Commision on 2009-03-12. The DC procedure for Sabufarm was also referred to the CMDh; the referral ended positively at 2008-03-03. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Hexal AG has applied for a marketing authorisation for **Sabumalin, Sanohex and Sabufarm** 100 microgram/dose suspension for pressurised inhalation. The three duplicate applications are hybrid applications as DCPs. The EU reference products referred to is Sultanol Dosier-Aerosol 100 ug/dose, Druckgasinhalation, suspension, (GlaxoSmithKline, DE). The reference product in SE is Ventoline Evohaler, 0.1 mg/dose (GlaxoSmithKline AB). The product contains "salbutamol as active substance. For approved indications see the Summary of Product Characteristics.

In the end of the DCP procedures, all three procedures were referred to the CMDh. Following a discussion in CMDh a CHMP referral was made for Sabumalin and Sanohex while the procedure for Sabufarm ended positively after the CMDh discussions. The CHMP referral ended positively and the positive commission decision was issued in March 2009.

II. QUALITY ASPECTS

II.1 Introduction

Sabumalin/Sanohex/Sabufarm is presented in the form of a suspension for pressurised inhalation containing 100 microgram/per dose of salbutamol corresponding to 120 microgram/dose of salbutamol sulphate. The excipients are anhydrous ethanol, oleic acid, and norflurane (HFA-134a). The suspension is filled into a pressurised aluminium container with a metering valve and plastic applicator which is fit into a plastic inhaler device.

II.2 Drug Substance

Salbutamol sulphate has a monograph in the Ph Eur.

Salbutamol sulphate is a white or almost white crystalline powder which is freely soluble in water, slightly soluble in ethanol, and very slightly soluble in dichloromethane. The structure of Sulbutamol sulphate has been adequately proven and its physico-chemical properties are sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Sabumalin/Sanohex/Sabufarm pressurised inhalation, suspension is formulated using excipients described in the current Ph Eur, except for norflurane which is controlled according to other EU requirements. The raw materials used in the product are of vegetable or synthetic origin or has demonstrated 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).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as solubility, hygroscopic properties, polymorphism, and particle size distribution. It has been shown that this product is able to deliver an aerosol for inhalation that is comparable *in-vitro* to that of the reference product.

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 drug product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and the data presented support the shelf life claimed in the SPC when stored below 30 °C in a horizontal or inverted position with the mouth piece pointing downwards. The drug product should be protected from heat, direct sunlight and frost.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of salbutamol sulphate are well known. As salbutamol sulphate is a widely used, well-known active substance, no further studies are required. Overview based on literature review is, thus, appropriate. The non-clinical overview refers to 154 publications from the years 1969-2006.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and is considered sufficient to support the application. All excipients are well-known and have further been used in inhalation products before.

There are no objections for approval of Sabumalin/Sanohex/Sabufarm from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The applicant has presented data from the literature covering the pharmacokinetics of salbutamol. The submitted presentation lack information on bioavailability from a HFA 134a formulation, dose- and time-proportionality, pharmacokinetics in target population and special populations (impaired organ function, elderly and paediatric populations). However, the presented data is considered sufficient.

The applicant submitted one pharmacokinetic study during the CHMP referral comparing the systemic exposure obtained after inhalation of the product applied for and the reference products referred to. The pharmacokinetic study was not performed using active charcoal and therefore measures complete systemic exposure obtained after administration and not

pulmonary deposition (pulmonary bioavailability). Bioequivalence was shown after administration of 800 µg salbutamol. The plasma concentration curves were also very similar and indicated similar early rate of absorption after the products were administered.

IV.2 Discussion on the clinical aspects

To show therapeutic equivalence, the applicant has submitted one pharmacodynamic equivalence study. The study was a single-dose, randomised, three-period crossover, open study. Included patients met diagnostic criteria for mild to moderate asthma according to the Global Initiative for Asthma (GINA) and had at least a 15% increase in FEV_1 after inhalation of 200 µg salbutamol. The subjects were either not on regular treatment with inhaled steroids or on a stable dose for 3 months. The primary endpoint was the area under the flow volume curve (AUC_{0-6}) of FEV_1. The treatment was one single dose of 100 µg of salbutamol from the test inhaler (Salbutamol) and the two reference inhalers (Sultanol and Ventoline). The results from the per protocol population showed similar values for the primary endpoint, see table below:

Table 1: Statistical analysis for AUC $_{0-6}$

Ratio	Estimate	90% CI
Parametric Analysis		
Salbutamol/Sultanol	102.8%	[99.9%; 105.7%]
Salbutamol/Ventoline	100.5%	[97.7%; 103.4%]

Since only one dose of each product has been tested it is not possible to know if there is a dose response relationship in the study, i.e. if the study is sensitive enough to discriminate between different doses. The Applicant has only provided some indirect evidence of sensitivity which is not considered sufficient. The open design was questioned by RMS and several CMSs. Some CMSs considered this issue as a potential risk for public health and in their opinion a double dummy technique is mandatory. The submitted clinical study does not show therapeutic equivalence, convincingly. Equivalent clinical efficacy has to be supported by quality documentation

Questions regarding the use in children have been raised by RMS and several CMSs. The Applicant has provided *in vitro* data on two named spacers. These data are considered as sufficient for an indication in children by the RMS provided equivalence with the reference products is shown with respect to adult use.

Clinical safety

The safety measurements are as such reassuring. However, they do not contribute to the assessment of equivalence. Also in the respect of safety, this study is insensitive to detect any differences between the treatments. The PK study submitted during the CHMP referral including systemic bioavailability assessment indicate similar systemic safety of the test and reference product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sabufarm: The conclusion reached in the CMDh referral procedure for Sabufarm was that the available pharmaceutical quality documentation supported equivalent efficacy and safety as the reference product.

Sabumalin and Sabuhex: The CHMP was of the opinion that based on the totality of the data submitted, a similar particle size distribution between the test and the reference product could be demonstrated. The pharmacokinetic bioequivalence data also confirmed that Sabumalin and the reference product possess the same systemic safety profile since bioequivalence in systemic levels (AUC and Cmax) have been shown. The CHMP concluded that the products are bioequivalent and that the benefit-risk ratio is positive.

The SPC, package leaflet and labelling are acceptable.
User testing of the package leaflet has been performed and is acceptable.

In conclusion, the risk/benefit ratio is considered positive and Sabumalin Sanohex / Sabufarm 100 µg/dose, pressurised inhalation, suspension was recommended for approval.

VI. APPROVAL

The decentralised procedure for Sabufarm was successfully finalised after a CMDh referral at 2008-03-03. The positive Commission Decisions for Sabumalin and Sabuhex were issued on the 2009-03-12.

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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)

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