Public Assessment Report
Scientific discussion

Salbutamol Sandoz
(salbutamol sulphate)

SE/H/971/01/DC

This module reflects the scientific discussion for the approval of Salbutamol Sandoz. The procedure was finalised at 2011-06-21. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Sandoz A/S has applied for a marketing authorisation for Salbutamol Sandoz, pressurised inhalation, suspension, 100 μg / dose claiming essential similarity to Sultanol Dosier-Aerosol, 100 μg/dose marketed in Germany by GlaxoSmith-Kline. The product contains salbutamol sulphate as active substance. For approved indications see the Summary of Product Characteristics. The reference products used in the bio-equivalence study are Sultanol Dosier-Aerosol, 100 μg/dose approved in Germany and Ventoline® N approved in France marketed by GlaxoSmith-Kline.

II. QUALITY ASPECTS

II.1 Introduction

Salbutamol sandoz is presented in the form of pressurised inhalation, suspension. Each metered dose contains 120 microgram of salbutamol sulphate which corresponds to 100 microgram of salbutamol. The excipients are norflurane (HFA 134a), anhydrous ethanol and oleic acid. The suspension for inhalation is filled in aluminium containers 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. The substance is a white or almost white crystalline powder which is freely soluble in water. The structure of salbutamol sulphate 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. 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

Salbutamol Sandoz, pressurised inhalation, suspension, 100 microgram/dose is formulated using excipients described in the current Ph Eur, except for the propellant norflurane which is controlled according to other EU requirements. All raw materials used in the product are of vegetable origin. The product development has taken into consideration the physico-chemical characteristics of the active substance, such as solubility 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 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 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

The pharmacodynamic, pharmacokinetic and toxicological properties of salbutamol are well known. As salbutamol is a widely used, well-known active substance, no further studies are required or are considered necessary. Furthermore, all excipients are well-known and have been used in inhalation products before. Risk assessments of each leachable/extractable substance at the concentrations specified are included and the specifications for each of the leachable/extractable substances from the product are considered acceptable. This product is not considered to increase the risk to the environment beyond or above that which may be caused by other salbutamol sulphate products.

IV. CLINICAL ASPECTS

IV.1 Discussion on the clinical aspects

Pharmacokinetics
Bioequivalence has been shown between the originator and Salbutamol Sandoz 100 ug after single-dose inhalation in healthy volunteers. The study was performed without charcoal and may thus be used for support of similar systemic safety. The efficacy is based on the pharmaceutical documentation.

Pharmacodynamics
Salbutamol is a well-known substance, used as bronchodilator for many years. It has a selective effect on the β2-receptors of the bronchi and produces bronchodilation within a few minutes. The pharmacodynamic properties of salbutamol are well described in the applicant’s Clinical Overview.

Clinical efficacy and safety
To support the application, the applicant has submitted one pharmacodynamic equivalence study. The study (Clinical study 2005-3-DOS-2) was also included in the dossier for Sabumalin, Sanohex and Sabufarm, SE/H/601-603/01/DC.

The study was a single-dose, randomised, three-period crossover, open study. Included patients were 18-65 years and met diagnostic criteria for mild to moderate asthma according to the Global Initiative for Asthma (GINA) and had at least a 15% increase in FEV₁ after inhalation of 200 µg salbutamol and an FEV₁ value of >60% and ≤85% of the predicted normal value. 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 (AUC₀₋₆) of FEV₁.

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 (n=22 subjects) showed similar values for the primary endpoint, see table below:
Table 1: Statistical analysis for AUC 0-6

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Estimate</th>
<th>90% CI</th>
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<tbody>
<tr>
<td>Parametric Analysis</td>
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<td></td>
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<tr>
<td>Salbutamol/Sultanol</td>
<td>102.9%</td>
<td>[99.9%; 105.7%]</td>
</tr>
<tr>
<td>Salbutamol/Ventoline</td>
<td>100.5%</td>
<td>[97.7%; 103.4%]</td>
</tr>
</tbody>
</table>

Since only one dose of each product has been tested it is not possible to evaluate if the study could discriminate between two doses, i.e. if the study is sensitive enough to show therapeutic equivalence or not. Therefore, the submitted study cannot be used to show equivalence. Furthermore the open design is questioned since, in our opinion, it would be possible to blind metered dose inhalers. The 95% CI should have been calculated for the difference in clinical equivalence trials according to guidelines. The safety measurements are as such reassuring, however 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.

In conclusion, the provided clinical study lacks proof of assay sensitivity, which means that it is not possible to know if the study can discriminate different doses of salbutamol. Therefore, the clinical study cannot be used to assess therapeutic equivalence. Thus, the therapeutic equivalence must rely on pharmaceutical and pharmacokinetic data.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the totality of the data submitted equivalence between the test and the reference product could be demonstrated. The *in vitro* data do not support an approval based only on pharmaceutical properties, but is considered sufficient in combination with a PK safety study. The pharmacokinetic data confirmed that the test and the reference product possess the same systemic safety profile since bioequivalence in system levels (AUC and Cmax) have been shown.

In conclusion, the risk/benefit ratio is considered positive. The product is recommended for approval.

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 making reference to Salbutamol 100 micrograms/dose pressurised inhalation, suspension, SE/H/601-602/01/DC. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Salbutamol Sandoz, pressurised inhalation, suspension, 100 μg / dose is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Salbutamol Sandoz, pressurised inhalation, suspension, 100 μg / dose was successfully finalised on 2011-06-21.
## Public Assessment Report – Update

<table>
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<th>Scope</th>
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<th>Product Information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
<th>Y/N (version)</th>
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