Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Stalpex 50 microgram/500 microgram/dose inhalation powder, pre-dispensed

(salmeterol xinafoate and fluticasone propionate)

Procedure Numbers: UK/H/6498/03/DC

UK Licence No: PL 25258/0296

Glenmark Pharmaceuticals Europe Limited

LAY SUMMARY

Stalpex 50 microgram/500 microgram/dose inhalation powder, pre-dispensed (salmeterol xinafoate and fluticasone propionate)

This is a summary of the Public Assessment Report (PAR) for Stalpex 50 microgram/500 microgram/dose inhalation powder, pre-dispensed (PL 25258/0296; UK/H/6498/003/DC). It explains how Stalpex 50 microgram/500 microgram/dose inhalation powder, pre-dispensed was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use this medicine.

For ease of reading, this product will be referred to as Stalpex in this Lay Summary.

For practical information about using Stalpex, the patient should read the package leaflet or contact their doctor or pharmacist.

What is Stalpex and what is it used for?

The application for Stalpex was submitted as a 'hybrid' application'. This means that it is similar to a 'reference medicine' containing the same active substances, already authorised in the UK, called Seretide Accuhaler 50 microgram / 500 microgram / dose inhalation powder, pre-dispensed (PL 10949/0316; Glaxo Wellcome UK Ltd).

Stalpex is used to help prevent breathing problems such as:

- Asthma
- Chronic Obstructive Pulmonary Disease (COPD)

This medicine should only be used to treat asthma, in adults and adolescent 12 years of age and older only and adults with COPD.

Stalpex helps to stop breathlessness and wheeziness coming on. However, this medicine should not be used to relieve a sudden attack of breathlessness or wheezing. If this happens, the patient needs to use a fast-acting 'reliever' ('rescue') inhaler, such as salbutamol. The patient should always have their fast-acting 'rescue' inhaler with them.

Stalpex is only available in one strength i.e. Salmeterol/Fluticasone 50 mcg /500 mcg. It is not available in the two lower strengths (i.e. salmeterol/ fluticasone 50/250 and 50/100 mcg). These strengths are available for other similar fixed-dose combination DPI products containing these two actives and currently available on the market. Therefore, when it is appropriate to titrate down to a lower strength not available for Stalpex a change to an alternative fixed-dose combination of salmeterol and fluticasone propionate containing a lower dose of the inhaled corticosteroid is required. Stalpex should not be used for patients with mild or moderate asthma, in whom a low dose of the inhaled corticosteroid, either alone or with a longacting β2 agonist, may be required.

How does Stalpex work?

Stalpex contains the active substances, salmeterol xinafoate and fluticasone propionate.

Salmeterol is a long-acting bronchodilator. This helps the airways in the lungs to stay open. This makes it easier for air to get in and out. The effects last for at least 12 hours.

Fluticasone propionate is a corticosteroid which reduces swelling and irritation in the lungs.

How is Stalpex used?

The pharmaceutical form of this medicine is an inhalation powder and the route of administration is inhalation through the mouth.

The patient should always use this medicine exactly as their doctor or pharmacist has told them. They should check with their doctor or pharmacist if they are not sure.

The patient should use Stalpex every day, until their doctor advises them to stop. The patient should not take more than the recommended dose.
The patient must not stop taking Stalpex or reduce the dose without talking to a doctor first.

Stalpex should be inhaled through the mouth into the lungs.

The recommended dose in adults and adolescnets aged 12 years and older with asthma is 50 microgram/500 microgram/dose, one inhalation twice a day.

The recommended dose of Stalpex in adults with COPD is 50 microgram /500 microgram /dose, one inhalation twice a day.

It is very important that the patient follows the doctor's instructions on how many inhalations to take and how often the medicine should be taken.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, instructions for use and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Stalpex have been shown in studies?

Studies to establish therapeutic equivalence of Stalpex to Seretide Accuhaler 50 microgram / 500 microgram / dose inhalation powder, pre-dispensed were submitted with this application. The results of these studies indicate that Stalpex has similar levels of safety and efficacy as Seretide Accuhaler 50 microgram / 500 microgram / dose inhalation powder, pre-dispensed. Therapeutic equivalence is defined as equivalent efficacy and safety when the new orally inhaled product for which a Marketing Authorisation is sought is compared with an appropriate reference orally inhaled product.

What are the possible side effects of Stalpex?

The most common side effect with Stalpex (which may affect more than 1 in 10 people) are headache and increased number of colds in patients with COPD.

The common side effects with Stalpex (which may affect up to 1 in 10 people) are:

- Thrush (sore, creamy-yellow, raised patches) in the mouth and throat, also sore tongue and hoarse voice and throat irritation. Rinsing the mouth out with water and spitting it out immediately and/or brushing the teeth after taking each dose of the medicine may help. A doctor may prescribe an anti-fungal medication to treat the thrush.
- Aching, swollen joints and muscle pain.
- Muscle cramps.

For the full list of all side effects reported with Stalpex, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Stalpex approved?

It was concluded that, in accordance with EU requirements, Stalpex has been shown to have comparable quality and to be therapeutically equivalent to Seretide Accuhaler 50 microgram / 500 microgram / dose inhalation powder, pre-dispensed. Therefore, the view was that, as for Seretide Accuhaler 50 microgram / 500 microgram / dose inhalation powder, pre-dispensed, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Stalpex?

A risk management plan (RMP) has been developed to ensure that Stalpex is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Stalpex including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Stalpex

Italy, Luxemburg, Malta, Republic of Ireland, Romania, The Netherlands and the UK agreed to grant a Marketing Authorisation on 26 September 2018. A Marketing Authorisation was granted to APC Instytut Sp. z o.o. (PL 46579/0003) on 23 October 2018.

Following a change of ownership procedure on 25 October 2018, the Marketing Authorisation was transferred to Glenmark Pharmaceuticals Europe Limited (PL 25258/0296).

The full PAR for Stalpex follows this summary.

This summary was last updated in December 2018.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Stalpex 50 microgram/500 microgram/dose inhalation powder, pre-dispensed (PL 25258/0296; UK/H/6498/003/DC), is approvable. The product is a Prescription Only Medicine (POM) indicated for:

Asthma

Stalpex is indicated for use in patients with severe asthma 12 years of age and older only.
Stalpex is indicated in the regular treatment of patients with **severe** asthma where use of a combination product (long-acting β2 agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled on a lower strength corticosteroid combination product

  or
- patients already adequately controlled on an inhaled corticosteroid in a high strength and a long-acting β2 agonist.

Chronic Obstructive Pulmonary Disease (COPD)

Stalpex is indicated for the symptomatic treatment of patients with COPD, with a FEV_1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Italy, Luxemburg, Malta, Republic of Ireland, Romania, The Netherlands as concerned member states (CMS). The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The application refers to the reference product Seretide Accuhaler 50 microgram / 500 microgram / dose inhalation powder, pre-dispensed, which was first authorised in the UK to Glaxo Wellcome UK Ltd (PL 10949/0316) on 01 February 1999.

This medicine contains the active substance salmeterol (as salmeterol xinafoate) and fluticasone propionate.

Salmeterol is a selective long-acting (12 hour) β_2 adrenoceptor agonist with a long side chain which binds to the exosite of the receptor.
Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β_2 agonists.

Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

The applicant has presented *in vitro* studies in their dossier as they claim that according to the guideline CPMP / EWP / 4151/00 Rev. 1 on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD), therapeutic equivalence can be demonstrated on the basis of the deposition profiles *in vitro* because all conditions described in paragraph 5 of the above guideline were fulfilled by the test product.
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 26 September 2018). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 46579/0003) for this product on on 23 October 2018.

Following a change of ownership procedure on 25 October 2018, this Marketing Authorisation was transferred to Glenmark Pharmaceuticals Europe Limited (PL 25258/0296).

II QUALITY ASPECTS

II.1 Introduction

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 47 micrograms of salmeterol (as salmeterol xinafoate) and 460 micrograms of fluticasone propionate. This corresponds to a pre-dispensed dose of 50 micrograms of salmeterol (as salmeterol xinafoate) and 500 micrograms fluticasone propionate.

The only ingredient used in this product is lactose monohydrate (which contains milk proteins). This excipient complies with its respective European Pharmacopoeia monograph. Satisfactory Certificate of Analysis and suitable batch analysis data have been provided.

Lactose monohydrate is the only excipient used that contains material of animal or human origin. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

The finished product is packaged in blisters made from polyamide (OPA)/aluminium/polyvinyl chloride (PVC)/aluminium/polyethylene terephthalate (PET)/paper contained in a molded plastic inhaler equipped with a mouthpiece and dose counter. The inhaler is packed in a cardboard box. One inhaler contains 60 inhalations.

The plastic devices are available in cardboard containers, which hold 1 x 60 dose, 2 x 60 dose, 3x 60 dose, 10 x 60 dose Stalpex.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

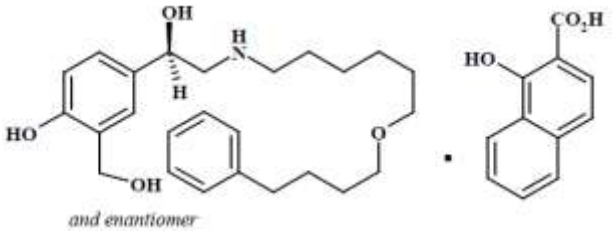
II.2 Drug Substance

Salmeterol xinafoate

INN: Salmeterol xinafoate

Chemical name: (R,S) 4-Hydroxy-a'-[[[6-(-l-phenyl butoxyl)hexyl]amino]-methyl]-1,3, benzenedimethanol, 1-hydroxy-2-naphthoate

Structure:



Molecular formula: $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$

Molecular weight: 604 g/mol

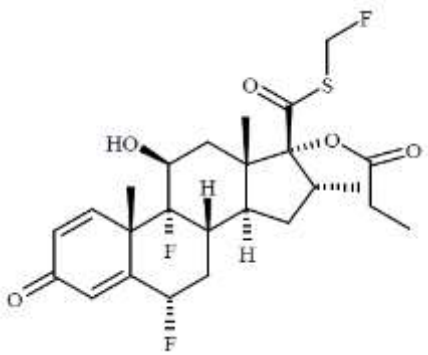
Description: A white or almost white powder

Solubility: Practically insoluble in water, soluble in methanol, slightly soluble in anhydrous ethanol.

Salmeterol xinafoate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, salmeterol xinafoate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Fluticasone propionate
INN: Fluticasone propionate
Chemical name:



Molecular formula: $C_{25}H_{31}F_3O_5S$
Molecular weight: 500.6 g/mol

Description: White or almost white powder.
Solubility: Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol (96 per cent).

Fluticasone propionate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, fluticasone propionate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development was to manufacture pre-dispensed powder for inhalation containing salmeterol xinafoate and fluticasone propionate as active ingredients, that are therapeutically equivalent to the refence product, Seretide Accuhaler 50 microgram / 500 microgram / dose inhalation powder, pre-dispensed (Glaxo Wellcome UK Ltd).

Comparative physicochemical properties have been demonstrated between the proposed and test products.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with commercial-scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years with the storage conditions 'Store below 30°C, in the original package in order to protect from moisture'.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical point of view.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of salmeterol xinafoate and fluticasone propionate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology data.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Stalpex 50 microgram/500 microgram/dose inhalation powder, pre-dispensed is intended to replace the reference product, it use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted or necessary for this type of application.

There are no objections to the approval of this application from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of salmeterol xinafoate and fluticasone propionate is well known and has been the subject of many publications.

The clinical development programme for this product (test product) was consistent with the step-wise approach as outlined in the Committee for Medicinal Products for Human Use (CHMP) Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment

of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in Children and Adolescents – CHMP/EWP/4151/00 Rev. 1 January 2009.

IV.2. Pharmacokinetics (PK)

The following *In-vivo* studies were conducted to evaluate equivalence between the test and reference products.

- Study 03SX2016 – A pharmacokinetic (PK) study without charcoal blockade
- Study 05SX2017– A pharmacokinetic (PK) study with charcoal blockade

Study 03SX2016

This is a randomised, single dose, open label, four-period, replicated, crossover study comparing 500/50 µg/dose inhalation powder of Fluticasone propionate/Salmeterol with Seretide Dysk (500 µg + 50 µg)/dose inhalation powder (GlaxoSmithKline Export Ltd) in a fasted state with charcoal blockade.

Objectives

- analysation of pharmacokinetic properties and bioequivalence of fluticasone propionate and salmeterol
- evaluation of the safety and tolerability of these formulations.

Subjects were not allowed to drink water from one hour before until one hour after dosing. No food was permitted until 4 hours after dosing.

A single dose of study medicinal products (500 µg + 50 µg) of fluticasone propionate and salmeterol, test product or reference product respectively, was administered by inhalation, while subjects were in the sitting position, according to the randomization table and under open-label conditions.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours post-dosing. The washout period between the treatment phases was 7 days.

The primary PK parameters are acceptable.

Results

Pharmacokinetic data for Test /Reference product - Salmeterol

Table 8. Pharmacokinetic data for Reference product (Seretide Dysk 500) - Salmeterol

PK parameter	Lambda_z	$T_{1/2}$	T_{max}	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	AUC_% Extrap_obs
N	83	83	83	83	83	83	83
Mean	0.079	9.897	0.067	185.267	199.331	242.736	18.589
SD	0.028	3.355	0.017	72.681	74.57	83.844	6.372
Min	0.04	4.23	0.05	46	66.17	92.44	9
Median	0.07	9.68	0.083	182.73	193.18	235.1	16.66
Max	0.16	19.13	0.083	346.83	418.99	482.96	46.25
CV%	35	33.9	24.725	39.2	37.4	34.5	34.3
Geometric Mean	0.074	9.353	0.065	169.493	185.752	228.922	17.651

Table 9. Pharmacokinetic data for Test product (Salmex) - Salmeterol

PK parameter	Lambda_z	$T_{1/2}$	T_{max}	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	AUC_% Extrap_obs
N	84	84	84	84	84	84	84
Mean	0.077	9.926	0.072	205.526	224.987	269.414	16.611
SD	0.028	3.018	0.021	64.538	69.189	79.982	5.204
Min	0.03	3.82	0.05	80.39	93.38	115.55	9.29
Median	0.07	9.81	0.083	218.83	221.69	265.7	15.71
Max	0.18	20.89	0.17	372.2	424.56	484.02	35.97
CV%	36.1	30.4	29.719	31.4	30.8	29.7	31.3
Geometric Mean	0.073	9.455	0.069	194.494	214.347	257.569	15.893

Pharmacokinetic data for Test /Reference product – fluticasone propionate

Table 10. Pharmacokinetic data for Reference product (Seretide Dysk 500) - fluticasone propionate

PK parameter	Lambda_z	$T_{1/2}$	T_{max}	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	AUC_% Extrap_obs
N	83	83	83	83	83	83	83
Mean	0.088	7.992	1.857	98.518	955.324	1092.962	12.508
SD	0.012	1.061	1.202	31.676	271.769	308.709	3.17
Min	0.06	5.46	0.13	29.06	334.47	391.29	5.24
Median	0.09	7.92	2	95.51	989.87	1121.37	12.48
Max	0.13	10.91	4	189.54	1729	1950.12	21.97
CV%	13.2	13.3	64.7	32.2	28.4	28.2	25.3
Geometric Mean	0.087	7.924	1.448	93.347	913.313	1044.566	12.096

Table 11. Pharmacokinetic data for Test product (Salmex) - fluticasone propionate

PK parameter	Lambda_z	$T_{1/2}$	T_{max}	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	AUC_% Extrap_obs
N	84	84	84	84	84	84	84
Mean	0.076	9.252	2.032	90.257	977.468	1177.327	16.776
SD	0.011	1.205	1.264	25.464	240.332	294.785	3.881
Min	0.06	5.91	0.17	34.17	431.62	518.21	6.39
Median	0.07	9.43	2	89.67	998.4	1189.35	17.19
Max	0.12	11.92	4	151.24	1585.57	1971.31	24.69
CV%	14.1	13	62.2	28.2	24.6	25	23.1
Geometric Mean	0.076	9.171	1.589	86.545	945.798	1137.661	16.28

Salemterol: The T/R C_{max} and AUC_{0-t} for salmeterol and fluticasone indicated equivalence of the test to the reference product. However, the validity of these results were questionable as for a number of individual subjects, AUC_{0-t}/ AUC0-∞ is <0.8 i. e the extrapolation is > 20%. As indicated in the EMA guidelines on bioequivalence, to provide a reliable estimate of the absorption, the sampling time should cover the plasma concentration time curve long enough – this is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity. In this study, the AUC derived from measurements is less than 80% AUC extrapolated to infinity for approximately 40% of participants (Salmeterol test and reference) and 33% of participants (Fluticasone test and reference). This suggests that the AUC has been inadequately characterised because of too short a sampling time and brings into question the validity of the results and does not allow equivalence to be conclusively demonstrated. The applicant was asked to (a) provide the AUC graphs for the individual particpants (b) to discuss and justify why despite the high proportion of participants having inadequately characterised AUC (extrapolation >20%), the applicant considers the results of this study valid.

At day 180, the applicant has provided the required graphs. For Salmeterol it is agreed that equivalence has been proven in this study without charcoal for this strength, when proxy measures for efficacy and safety are considered as advocated by the PKWP Q&A i.e. AUC_{0-30} min as a surrogate for efficacy and AUC_{0-t} for safety.

Fluticasone: The T/R C_{max} and AUC_{0-t} indicate equivalence of the test to the reference product. However, the validity of these results were questionable as for a number of individual subjects, AUC_{0-t}/ $AUC_{0-\infty}$ is <0.8 i. e the extrapolation is > 20%. As indicated in the EMA guidelines on bioequivalence, to provide a reliable estimate of the absorption, the sampling time should to cover the plasma concentration time curve long enough – this is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity. In this study, the AUC derived from measurements is less than 80% AUC extrapolated to infinity for approximately 33% of participants (Fluticasone test and reference). This suggests that the AUC has been inadequately characterised because of too short a sampling time and brings into question the validity of the results and does not allow equivalence to be conclusively demonstrated.

The applicant was asked to (a) provide the AUC graphs for the individual particpants (b) to discuss and justify why despite the high proportion of participants having inadequately characterised AUC (extrapolation >20%), the applicant considers the results of this study valid.

At day 180, for Fluticasone, as pointed out by the applicant, it is agreed that less than 20% of the total observations had $AUC_{0-t}/AUC_{0-\infty}$ < 80%. Therefore, no concern remains regarding this component at this strength.

No new or unexpected safety concerns are raised.

Study 03SX2017
This is a randomised, single dose, open label, four-period, replicated, crossover study comparing 500/50 µg/dose inhalation powder of Fluticasone propionate/Salmeterol with Seretide Dysk (500 µg + 50 µg)/dose inhalation powder (GlaxoSmithKline Export Ltd) in a fasted state with charcoal blockade.

Objectives
- analysation of pharmacokinetic properties and bioequivalence of fluticasone propionate and salmeterol
- evaluation of the safety and tolerability of these formulations.

Subjects were not allowed to drink water from one hour before until one hour after dosing. No food was permitted until 4 hours after dosing.

A single dose of study medicinal products (500 µg + 50 µg) of fluticasone propionate and salmeterol, test product or reference product respectively, was administered by inhalation, while subjects were in the sitting position, according to the randomization table and under open-label conditions.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours post-dosing. The washout period between the treatment phases was 7 days.

The primary PK parameters are acceptable.

Results

Pharmacokinetic data for Test /Reference product - Salmeterol

Table 3. Pharmacokinetic data for Reference product (Seretide Dysk 500) – Salmeterol

PK parameter	Lambda_z	HL_Lambda_z	Tmax	Cmax	AUClast	AUCINF_obs	AUC_%Extrap_obs
N	86	86	86	86	86	86	86
Mean	0.0716	10.235	0.065	192.624	202.886	231.957	12.807
SD	0.016	2.578	0.017	71.21	56.907	60.985	4.49
Min	0.0415	6.26	0.05	55.39	92.51	115.53	6.01
Median	0.0724	9.57	0.05	190.54	195.03	228.12	11.88
Max	0.1108	16.69	0.083	365.32	346.39	372.14	24.94
CV%	22.4	25.2	25.3	37	28	26.3	35.1
Geometric Mean	0.0697	9.945	0.063	178.275	195.003	223.949	12.078
CV% Geometric Mean	24.01	24.01	25.84	43.42	29.26	27.48	35.47

Table 4. Pharmacokinetic data for Test product (Salmex) – Salmeterol

PK parameter	Lambda_z	HL_Lambda_z	Tmax	Cmax	AUClast	AUCINF_obs	AUC_%Extrap_obs
N	86	86	86	86	86	86	86
Mean	0.0708	10.506	0.068	220.18	229.17	258.687	11.826
SD	0.0181	2.999	0.021	76.132	65.285	67.404	4.328
Min	0.0356	5.61	0.017	76.5	76.3	94.02	3.44
Median	0.072	9.62	0.083	217.44	226.9	252.04	11.19
Max	0.1236	19.49	0.167	460.21	429.7	449.25	25.24
CV%	25.5	28.5	31.4	34.6	28.5	26.1	36.6
Geometric Mean	0.0684	10.128	0.065	206.88	220.159	249.992	11.052
CV% Geometric Mean	27.26	27.26	32.48	37.83	29.47	27.18	39.23

In 7% (6/86) of the observations after dosing the reference formulation and 3,5% (3/86) of the observations the AUC_{last} covers less than 80% of AUCINF obs.

Pharmacokinetic data for Test /Reference product – fluticasone propionate

Table 5. Pharmacokinetic data for Reference product (Seretide Dysk 500) – fluticasone propionate

PK parameter	Lambda_z	HL_Lambda_z	Tmax	Cmax	AUClast	AUCINF_obs	AUC_%Extrap_obs
N	86	86	86	86	86	86	86
Mean	0.0764	9.825	1.797	100.781	1007.989	1069.975	6.291
SD	0.0237	2.576	0.974	33.263	339.076	343.42	3.364
Min	0.043	4.17	0.5	48.56	176.87	204.2	2.04
Median	0.0688	10.08	2	91.47	972.09	1014.48	5.28
Max	0.1661	16.12	4	196.57	1630.73	1717.06	19.41
CV%	31	26.2	54.2	33	33.6	32.1	53.5
Geometric Mean	0.0733	9.462	1.542	95.751	939.945	1003.715	5.577
CV% Geometric Mean	29	29	62.23	32.85	42.63	40.66	51.38

Table 6. Pharmacokinetic data for Test product (Salmex) – fluticasone propionate

PK parameter	Lambda_z	HL_Lambda_z	Tmax	Cmax	AUClast	AUCINF_obs	AUC_%Extrap_obs
N	86	86	86	86	86	86	86
Mean	0.0715	10.396	1.875	87.179	1009.442	1069.641	6.053
SD	0.0238	2.407	1.032	21.856	303.704	307.637	3.048
Min	0.0392	3.09	0.5	44.17	224.83	244.28	2.19
Median	0.0651	10.64	1.5	84.19	1022.14	1101.83	5.06
Max	0.2247	17.7	4	159.58	1651.56	1761.79	16.07
CV%	33.2	23.2	55.1	25.1	30.1	28.8	50.4
Geometric Mean	0.0688	10.082	1.597	84.528	953.378	1015.346	5.431
CV% Geometric Mean	26.67	26.67	63.99	25.56	38.03	36.18	48.08

Salmeterol: The primary PK parameters between test and reference indicate bioequivalence. It is noted that a longer sampling duration (48 hours) was adopted in this study compared to the study done without charcoal. The time concentration curve in this study is better defined. A low number of subjects had extrapolation of $AUC_{0-\infty}$ residual > 20%. This is acceptable. Bioequivalence of the salmeterol component in this study is demonstated.

Fluticasone: The C_{max} and AUC_{0-t} met bioequivalence criteria. It is noted that a longer sampling duration (48 hours) was adopted in this study compared to the study done without charcoal. There the time concentration curve in this study is better defined. None of the subjects had extrapolation of $AUC_{0-\infty}$ residual > 20% of the entire AUC. This indicates that the AUC was adequately captured. Bioequivlaence of the Fluticasone component in this study is demonstrated.

IV.4 Clinical efficacy

No new efficacy data were submitted, and none were required for applications of this type.

IV.5 Clinical safety

No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Stalpex 50 microgram/500 microgram/dose inhalation powder, pre-dispensed.

A summary of safety concerns as approved in the RMP, is listed below:

Important identified risks	• Pneumonia in COPD patient population • Exacerbation of asthma which may be life-threatening • Systemic effects of inhaled corticosteroids, including Cushing's syndrome, adrenal suppression and acute adrenal crisis • Interaction with CYP450 3A4 inhibitors leading to increased salmeterol and fluticasone exposure • Hypersensitivity reactions including anaphylactic reactions • Cardiac arrhythmias, especially in patients with severe cardiovascular disorders, heart rhythm abnormalities and those with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium • Angina pectoris • Paradoxical bronchospasm • Growth retardation in paediatrics
Important potential risks	• Use in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway • Pneumonia in asthma patient population • Risk of overdose in patients that need a lower dose than the authorised dose
Missing information	• Use in children < 4 years • Breastfeeding women • Patients with hepatic impairment

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. This is satisfactory.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

V 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 English.

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.

VI Overall conclusion, benefit/risk assessment and recommendation

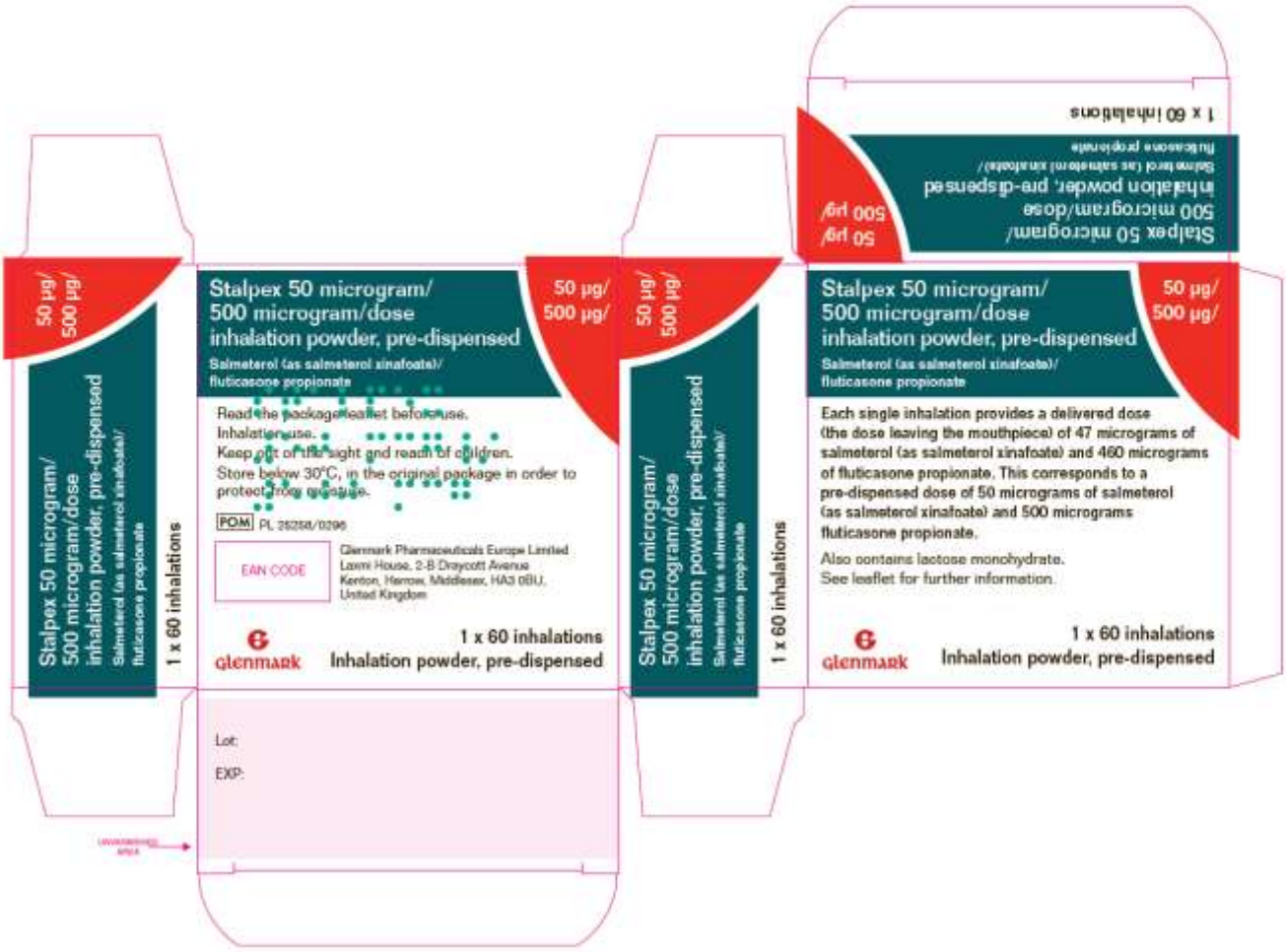
Stalpex is only available in one strength i.e. Salmeterol/Fluticasone 50 mcg /500 mcg. It is not available in the two lower strengths (i.e. salmeterol/ fluticasone 50/250 and 50/100 mcg). These strengths are available for other similar fixed-dose combination DPI products containing these two actives and currently available on the market. Therefore, when it is appropriate to titrate down to a lower strength not available for Stalpex a change to an alternative fixed-dose combination of salmeterol and fluticasone

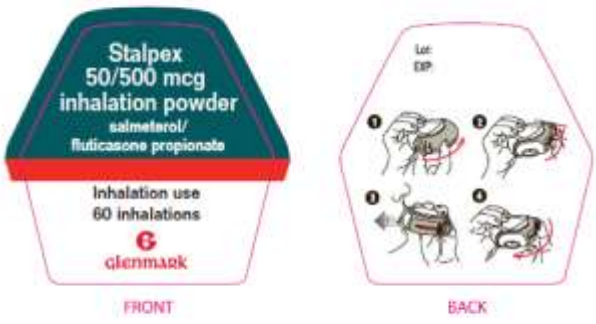
propionate containing a lower dose of the inhaled corticosteroid is required. Stalpex should not be used for patients with mild or moderate asthma, in whom a low dose of the inhaled corticosteroid, either alone or with a longacting β2 agonist, may be required.

The use of salmeterol and fluticasone in asthma and COPD is well established. The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with salmeterol xinafoate and fluticasone propionate is considered to have demonstrated the therapeutic value of the compounds. The product is therapeutically equivalent to the marketed reference product and their risks and benefits are considered similar The benefit risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Stalpex 50 microgram/500 microgram/dose inhalation powder, pre-dispensed is presented below:





Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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)