COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Soprobec 50 µg, 100 µg, 200 µg and 250 µg per actuation pressurised inhalation solution (beclometasone dipropionate)

NL/H/5085/001-004/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Soprobec 50 µg, 100 µg, 200 µg and 250 µg per actuation pressurised inhalation solution. The procedure was finalised in the United Kingdom (UK/H/6818/001-004/DC). After a transfer in 2019, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

Decentralised Procedure

Soprobec 50 micrograms per actuation pressurised inhalation solution

Soprobec 100 micrograms per actuation pressurised inhalation solution

Soprobec 200 micrograms per actuation pressurised inhalation solution

Soprobec 250 micrograms per actuation pressurised inhalation solution

(Beclometasone dipropionate)

Procedure No: UK/H/6818/001-004/DC

UK Licence Number: PL 25258/0278-0281

Glenmark Pharmaceuticals Europe Limited

LAY SUMMARY

Soprobec 50 micrograms per actuation pressurised inhalation solution
Soprobec 100 micrograms per actuation pressurised inhalation solution
Soprobec 200 micrograms per actuation pressurised inhalation solution
Soprobec 250 micrograms per actuation pressurised inhalation solution

(Beclometasone dipropionate)

This is a summary of the Public Assessment Report (PAR) for Soprobec 50 micrograms per actuation pressurised inhalation solution (PL 25258/0278; UK/H/6818/001/DC), Soprobec 100 micrograms per actuation pressurised inhalation solution (PL 25258/0279; UK/H/6818/002/DC), Soprobec 200 micrograms per actuation pressurised inhalation solution (PL 25258/0280; UK/H/6818/003/DC) and Soprobec 250 micrograms per actuation pressurised inhalation solution (PL 25258/0281; UK/H/6818/004/DC). It explains how Soprobec 50, 100, 200 and 250 micrograms per actuation pressurised inhalation solution were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

The products will be collectively referred to as 'Soprobec' throughout the remainder of this PAR.

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

What is Soprobec and what is it used for?
Soprobec are 'hybrid generic medicines'. This means that they are similar to reference medicines containing the same active substance and already authorised in the European Union (EU) called Becotide 50, 100 and 200mcg Inhalers and Becloforte 250mcg Inhaler (Glaxo Wellcome UK Limited, UK).

Soprobec pressurised inhalation solution is used to help prevent the symptoms of mild, moderate or severe asthma.

How does Soprobec work?
The active ingredient, beclomethasone dipropionate, is one of a group of medicines called corticosteroids which are often referred to simply as steroids. Steroids have an anti-inflammatory action reducing the swelling and irritation in the walls of the small air passages in the lungs, and so ease breathing problems.

How is Soprobec used?
The pharmaceutical form of this medicine is a pressurised inhalation, solution, which is supplied in an inhaler. The route of administration of Soprobec is inhalation through the mouth.

Soprobec is available in 4 different strengths. The patient's doctor will have decided which strength they need.

Soprobec 200 and Soprobec 250 are not suitable for children.

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

Instructions for using the inhaler are given in the dosage section of the package leaflet available on the MHRA website. It takes a few days for the inhaler to work. It is very important that the patient uses it regularly.

The patient should not stop treatment even if they feel better unless told to do so by their doctor. The patient should **not stop** using their inhaler abruptly.

While the patient is using Soprobec, their doctor will want to check their asthma regularly by carrying out simple breathing tests and may need to carry out blood tests from time to time.

Dosage:
The starting dose will depend on how severe the patient's asthma is and will be decided by their doctor. The patient's doctor will prescribe the lowest dose of Soprobec that will control the patient's symptoms.

A device called a Volumatic spacer should always be used when:

- adults, the elderly and adolescents 16 years of age and older are taking total daily doses of Soprobec of 1,000 micrograms or more,
- when Soprobec is used in children and adolescents 15 years of age and under whatever dose has been prescribed.

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

For further information on how Soprobec is used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Soprobec have been shown in studies?
As Soprobec are hybrid generic applications, studies have been limited to tests to determine that these medicines are pharmaceutically equivalent, demonstrating equivalent physiochemical characteristics to the reference medicines. On this basis, it is considered that Soprobec is therapeutically equivalent to Becotide 50, 100 and 200mcg Inhalers and Becloforte 250mcg Inhaler (Glaxo Wellcome UK Limited, UK). Two medicines are therapeutically equivalent when they produce the same measure of therapeutic effect in the body.

What are the possible side effects of Soprobec?
Like all medicines, Soprobec can cause side effects, although not everybody gets them.

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

For the full list of all side effects reported with Soprobec, see section 4 of the package leaflet available on the MHRA website.

Why was Soprobec approved?
The MHRA decided that the benefits of Soprobec are greater than their risks and recommended that they could be approved for use.

What measures are being taken to ensure the safe and effective use of Soprobec?
A risk management plan (RMP) has been developed to ensure that Soprobec is used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet for Soprobec 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 Soprobec
Marketing Authorisations were granted in the UK on 20 December 2018.

The full PAR for Soprobec follows this summary.

This summary was last updated in February 2019.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Glenmark Pharmaceuticals Europe Limited Marketing Authorisations for the medicinal product Soprobec (PL 25258/0278-0281; UK/H/6818/001-004/DC) on 20 December 2018. The product is a prescription only medicine (POM).

Soprobec is indicated for the prophylactic management of mild, moderate, or severe asthma in adults or children:

- *Mild asthma*: Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular basis
- *Moderate asthma*: Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone
- *Severe asthma:* Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms

The applications were submitted using the Decentralised procedure (DCP) with the UK as Reference Member State (RMS) and Luxembourg as Concerned Member State (CMS); subsequently during the procedure, Luxembourg was withdrawn as a CMS on 24 July 2018. The applications for Soprobec were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. This is in line with CMDh guidance, where locally applied products such as these inhalation products are considered as products where "bioequivalence cannot be demonstrated through bioavailability studies", so these marketing authorisation applications (MAAs) are submitted as hybrid applications. For the purposes of satisfying data exclusivity, the applications refer to the reference products Becotide Inhalers (50, 100 & 200mcg; PL 10949/0058-60) and Becloforte Inhaler (250mcg; PL 10949/0065) which were authorised following change of ownership procedures of the originator products Becotide 50, 100 and 200 Inhaler (PL 00045/0089R, PL 00045/0131 and PL 00045/0152; Allen & Hanburys Limited, UK) and Becloforte 250 Inhaler (PL 00045/0125; Allen & Hanburys Limited UK) which were initially approved in the UK, based on a full dossier, on 10 October 1972 (Becotide 50 mcg), 23 June 1986 (Becotide 100mcg), 25 April 1991 (Becotide 200mcg) and 12 May 1982 (Becloforte 250 mcg). These products have been discontinued since 2006 hence it is not practically feasible to use them in studies to demonstrate equivalence.

The applications therefore also refer to clinical studies included into the dossier of Clenil Modulite 50, 100, 200, 250 micrograms per actuation pressurised inhalation solution (PL 08829/0133-0136), which were approved, in the UK, based on abridged applications claiming essential similarity with Becotide, by Chiesi Limited on 29 June 2006. Clenil Modulite has been developed to contain a CFC-free propellant, i.e. HFA 134a – Norflurane, in order to replace CFC containing Becotide inhalers which were to be removed from the market due to their ozone-depleting propellants.
The dossier for Clenil Modulite is supported by clinical pharmacokinetic studies to establish equivalence with Beclometasone CFC inhaler (Glaxo Wellcome) as well as clinical efficacy studies to demonstrate non-inferiority in the comparison of BDP HFA with BDP CFC with regard to the efficacy and safety of efficacy and safety of BDP HFA with BDP CFC, in adults (and a separate study in children) with mild and mild to moderate asthma.

The therapeutic equivalence of Beclometasone Pressurised Inhalation 50 mcg, 100 mcg, 200 mcg and 250 mcg per actuation with Clenil Modulite 50, 100, 200, 250 micrograms per actuation is claimed to have been demonstrated via *in vitro* studies.

Although no new clinical studies have been submitted, it can be assumed that the studies listed in the submitted dossier complied to the requisite standards as these have been published in peer-reviewed literature or have been part of previous regulatory dossiers.

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B-17-MP), which has potent topical anti- inflammatory activity.

No new non-clinical or clinical studies were conducted, which is acceptable given that the products are generic hybrid applications of approved reference medicinal products containing a well-known active substance.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 20 November 2018. After a subsequent national phase, licences were granted in the UK on 20 December 2018.

II QUALITY ASPECTS

II.1 Introduction

Each actuation contains 50, 100, 200 or 250 micrograms of the active ingredient beclomethasone dipropionate (metered [ex-valve] dose). Other ingredients consist of the pharmaceutical excipients norflurane (HFA-134a), anhydrous ethanol and glycerol.

Sprobec 50 micrograms per actuation pressurised inhalation solution is supplied in an aluminium canister fitted with a metering valve, cream coloured actuator and dark brown colour dust cap. Each inhaler delivers 200 actuations.

Soprobec 100 micrograms per actuation pressurised inhalation solution is supplied in an aluminium canister fitted with a metering valve, grey coloured actuator and light pink colour dust cap. Each inhaler delivers 200 actuations.

Soprobec 200 micrograms per actuation pressurised inhalation solution is supplied in an aluminium canister fitted with a metering valve, light brown coloured actuator and cream colour dust cap. Each inhaler delivers 200 actuations.

Soprobec 250 micrograms per actuation pressurised inhalation solution is supplied in an aluminium canister fitted with a metering valve, maroon coloured actuator and grey colour dust cap. Each inhaler delivers 200 actuations.

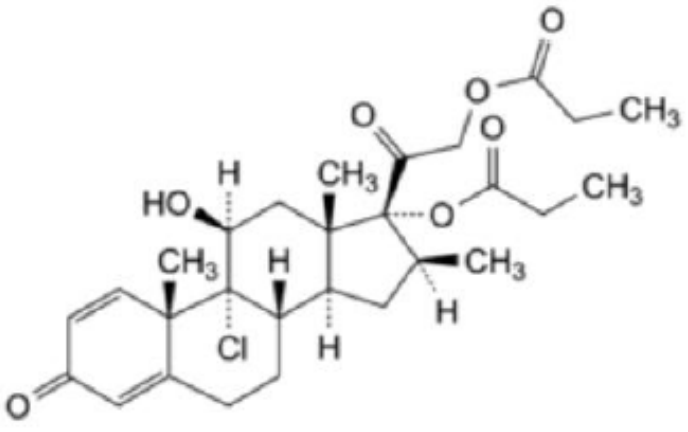
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Beclometasone dipropionate

Chemical name: 9-Chloro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-diene-17,21-diyl dipropanoate.

Structure:



Molecular formula: $C_{28}H_{37}ClO_7$

Molecular weight: 521.0

Appearance: White or almost white, crystalline powder.

Solubility: Practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96 per cent).

Beclometasone dipropionate in the subject of a European Pharmacopoeia monograph.

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

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop stable, equivalent inhalation aerosol formulations of beclometasone pressurised inhalation 50,100,200 and 250 micrograms per actuation for oral inhalation, which is pharmaceutically equivalent to the reference products Clenil Modulite 50, 100, 200, 250 micrograms per actuation. A satisfactory account of the pharmaceutical development has been provided.

Comparative physicochemical data have been provided for the proposed and reference products.

All excipients comply with their respective European Pharmacopoeia (Ph.Eur) monograph. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

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

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished Product Specification

The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which 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 the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions 'As with most inhaled medicines in aerosol canisters, the therapeutic effect may decrease when the canister is cold. Protect from frost and direct sunlight. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister.'

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 these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of beclomethasone dipropionate 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.

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 Ecotoxicity/environmental risk assessment (ERA)
Since Soprobec is intended as an equivalent to an existing product, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects
There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of beclomethasone dipropionate is well-known. No new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of beclomethasone dipropionate.

IV.2 Pharmacokinetics
No clinical pharmacokinetic studies have been submitted with this dossier. The applicant claims *in vitro* equivalence obviating the need for a clinical study. The applicant claims that the requirements for formulation and device similarity between test and reference products are met. Therefore, in line with the CPMP/EWP/4151/00 Rev. 1, 2009 guideline the applicant has now submitted an 'abridged' application that contains only comparative *in vitro* data to substantiate a claim of therapeutic equivalence with the reference product. As *in vitro* equivalance is demonstrated satisfactorily, no clinical pharmacokinetic study to establish equivalence is required.

The indication proposed for the Applicant's beclometasone dipropionate pressurised inhalation solution is the same as that approved for the clinical reference product Clenil Modulite. This is acceptable.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted, and none were required for applications of this type. An overview of the efficacy of beclometasone has been presented in the dossier and is summarised in the clinical assessment report.

IV.5 Clinical safety
No new safety data were submitted and none are required. An overview of the safety of beclometasone has been presented in the dossier and is summarised in the clinical assessment report.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
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 Soprobec.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Important identified risks	Systemic glucocorticosteroid effects: Adrenal suppression, cataract, glaucoma, psychiatric disorders, decrease in bone mineral density Systemic glucocorticosteroid effect: Growth retardation in children and adolescents Ocular events (cataract, glaucoma, ocular hypertension, central serous chorioretinopathy)
Important potential risk	Off-label use of the 200 and 250 strengths in children
Missing information	Use during pregnancy and breastfeeding

The Applicant proposes routine Pharmacovigilance and routine risk minimisation measures for all safety concerns, which is accepted.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

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.

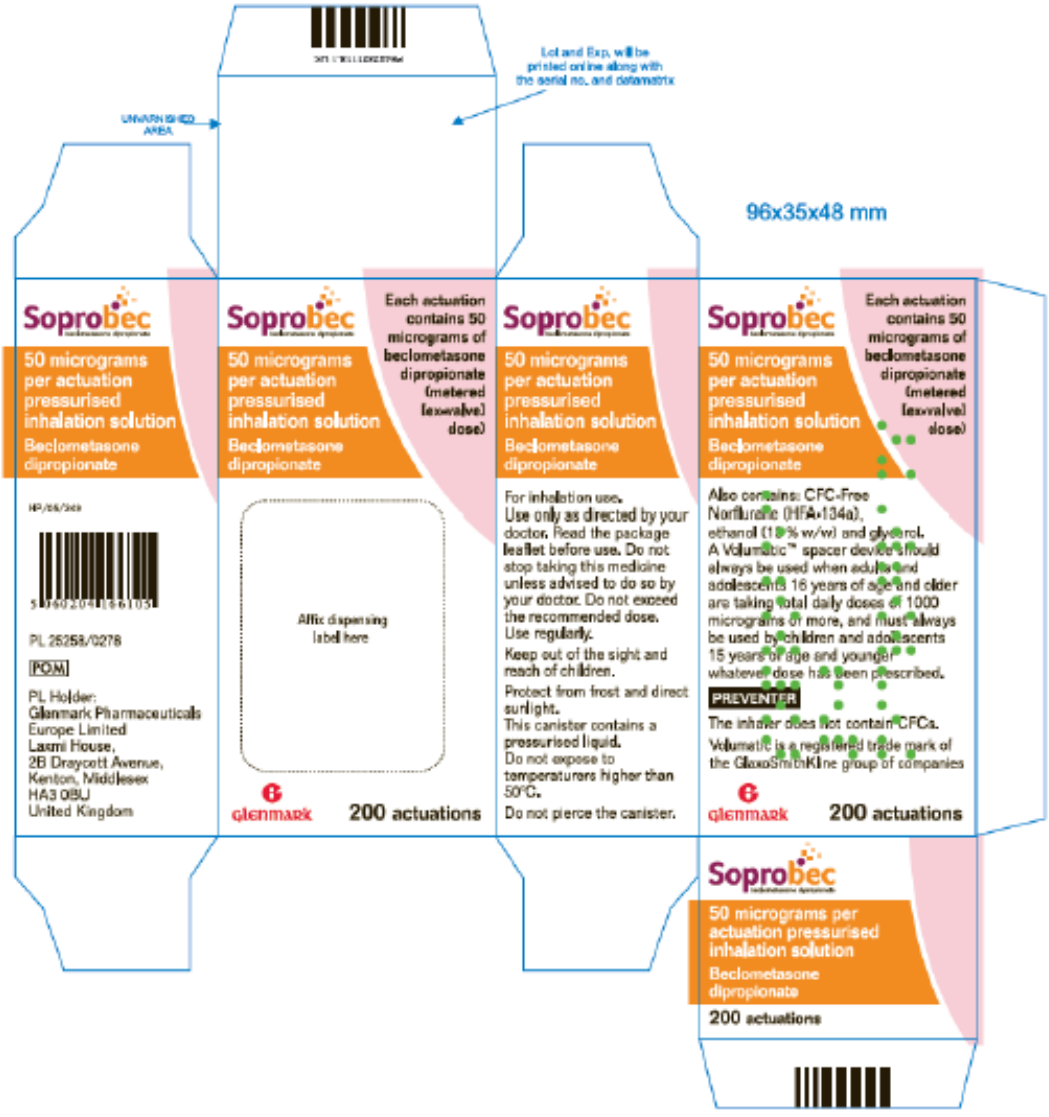
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with beclometasone dipropionate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk 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 (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:



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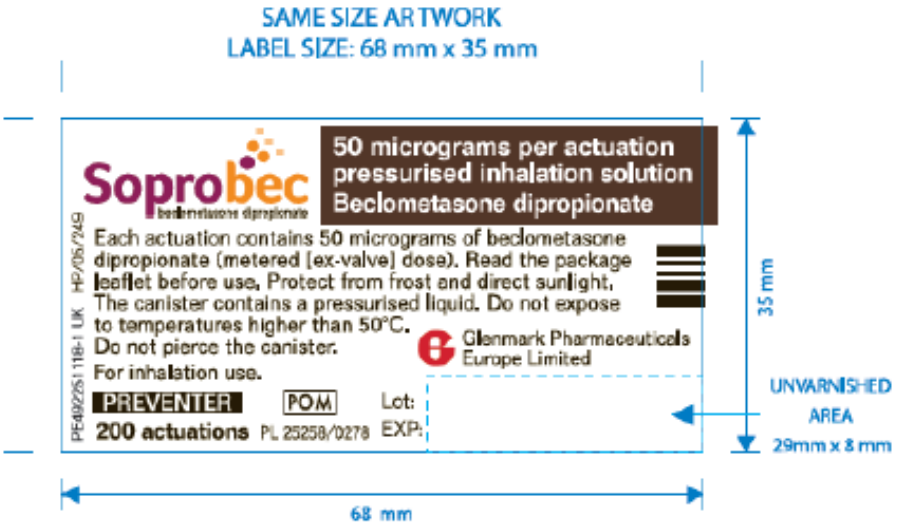
Soprobec
(numeral sign) 50
micrograms

(Pharmabraille UK 28.35 pts)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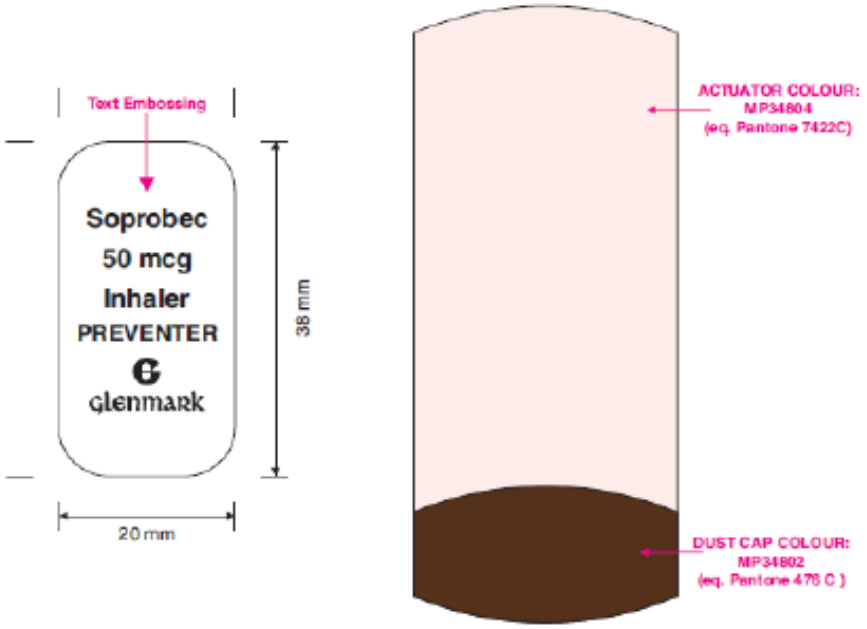
LABEL SIZE: 68 mm x 35 mm
Soprobec
beclometasone dipropionate
50 micrograms per actuation
pressurised inhalation solution
Beclometasone dipropionate
Each actuation contains 50 micrograms of beclometasone dipropionate (metered [ex-valve] dose). Read the package leaflet before use. Protect from frost and direct sunlight. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.
For inhalation use.
Glenmark Pharmaceuticals Europe Limited
PREVENTER
POM
Lot:
200 actuations
PL 25258/0278
EXP:
PE492/25 I 118-I UK HP/05/749
35 mm
UNVARNISHED AREA
29mm x 8 mm
68 mm


Text Embossing
Soprobec
50 mcg
Inhaler
PREVENTER
glenmark
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20 mm
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DUST CAP COLOUR:
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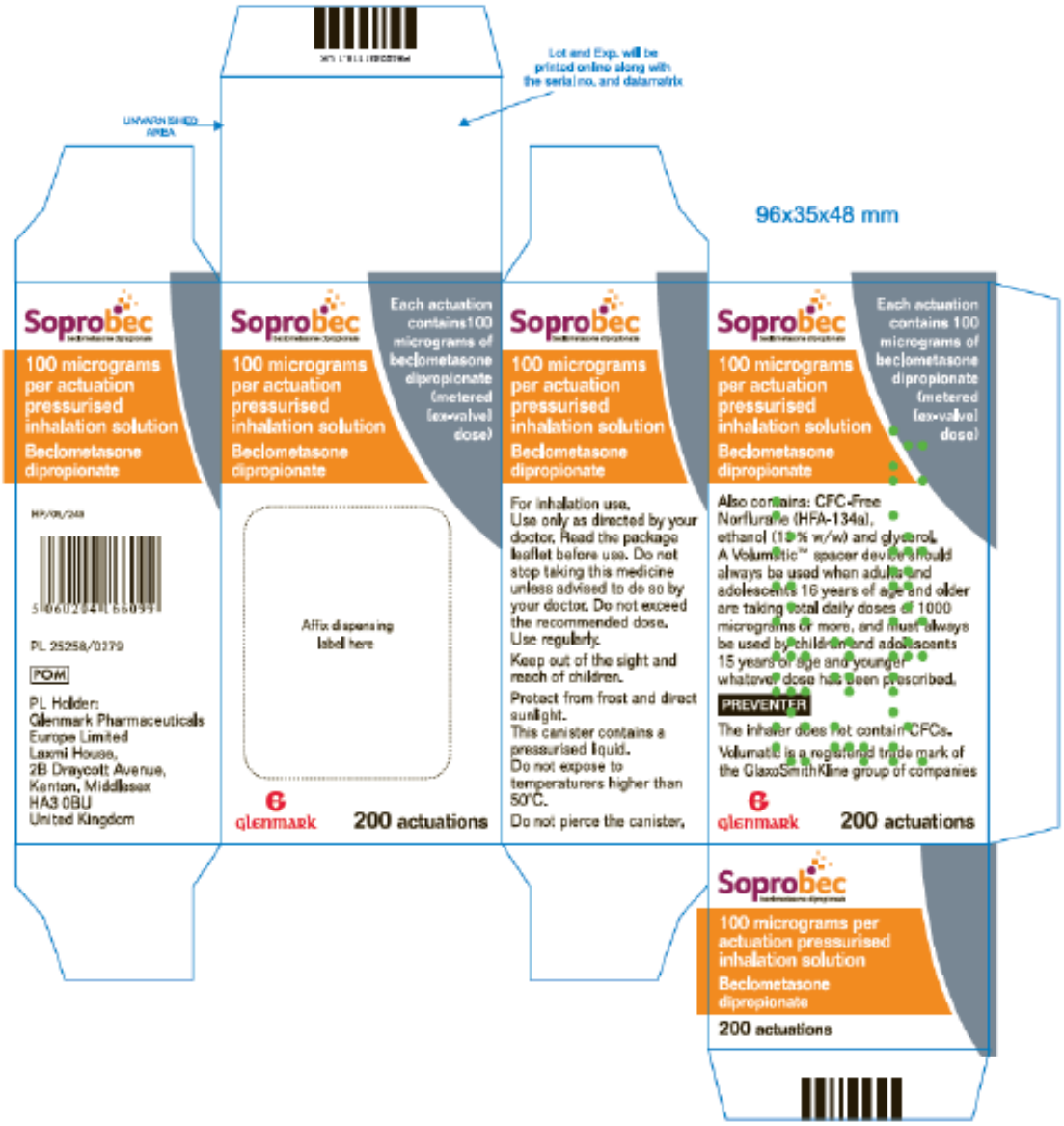

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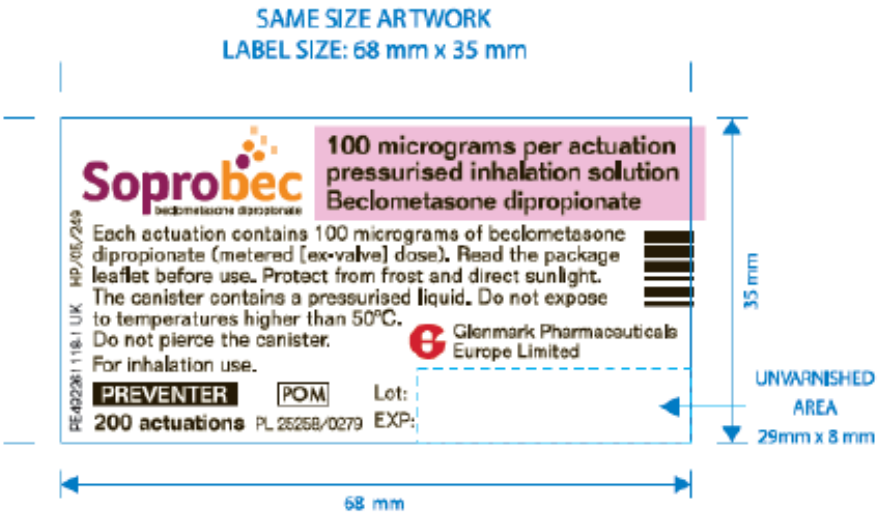
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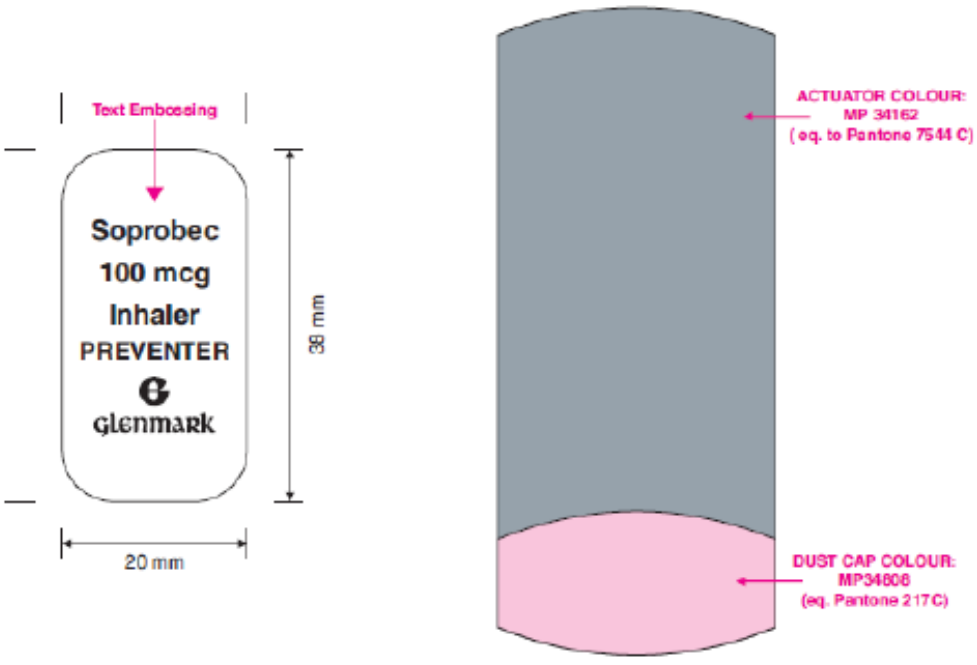
Soprobec
beclometasone dipropionate
100 micrograms per actuation
pressurised inhalation solution
Beclometasone dipropionate
Each actuation contains 100 micrograms of beclometasone dipropionate (metered [ex-valve] dose). Read the package leaflet before use. Protect from frost and direct sunlight. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister. For inhalation use.
PREVENTER
POM
Lot:
200 actuations
PL 25258/0279
EXP:
Glenmark Pharmaceuticals Europe Limited
PE422361116-I UK HP/05/249
35 mm
UNVARNISHED AREA
29mm x 8 mm
68 mm


Text Embossing
Soprobec
100 mcg
Inhaler
PREVENTER
glenmark
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20 mm
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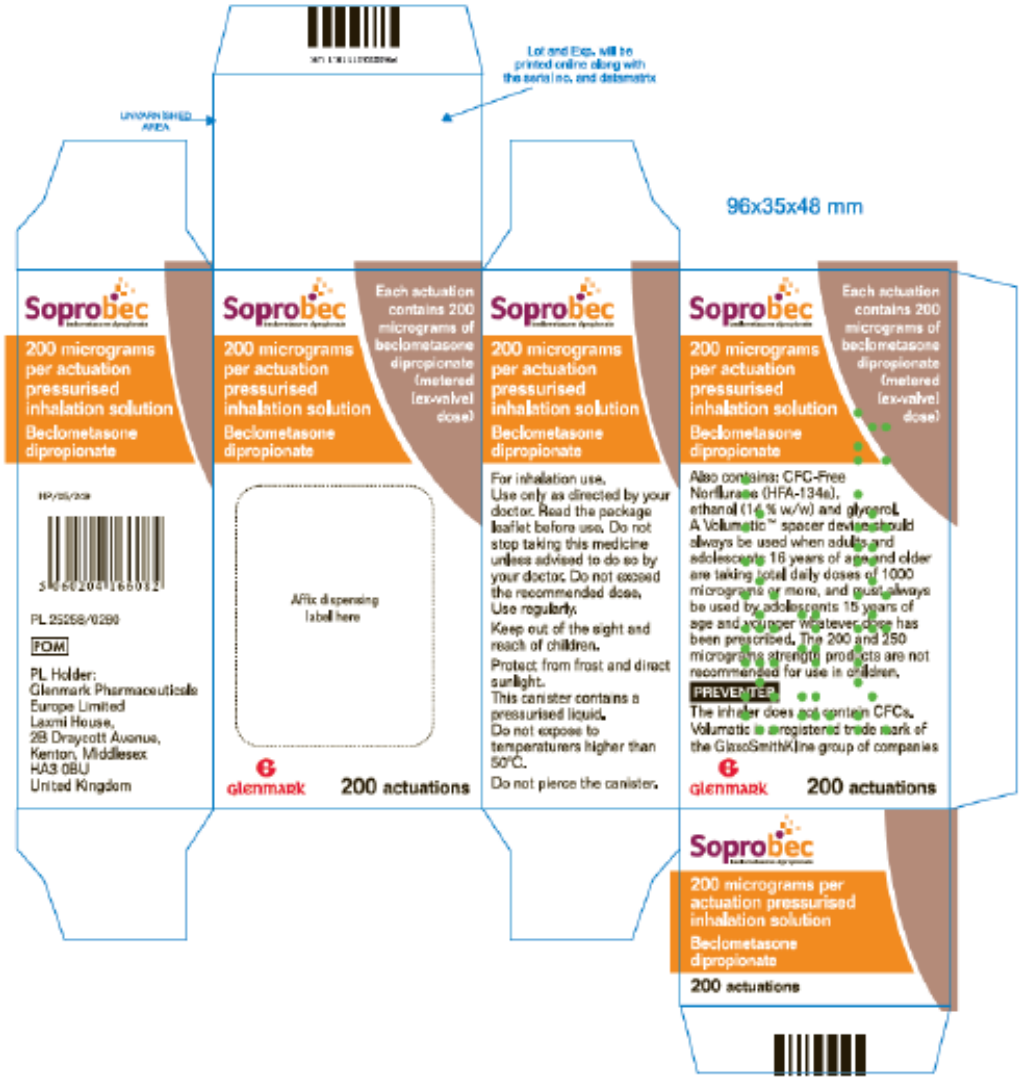
(eq. to Pantone 7544 C)
DUST CAP COLOUR:
MP34806
(eq. Pantone 217C)



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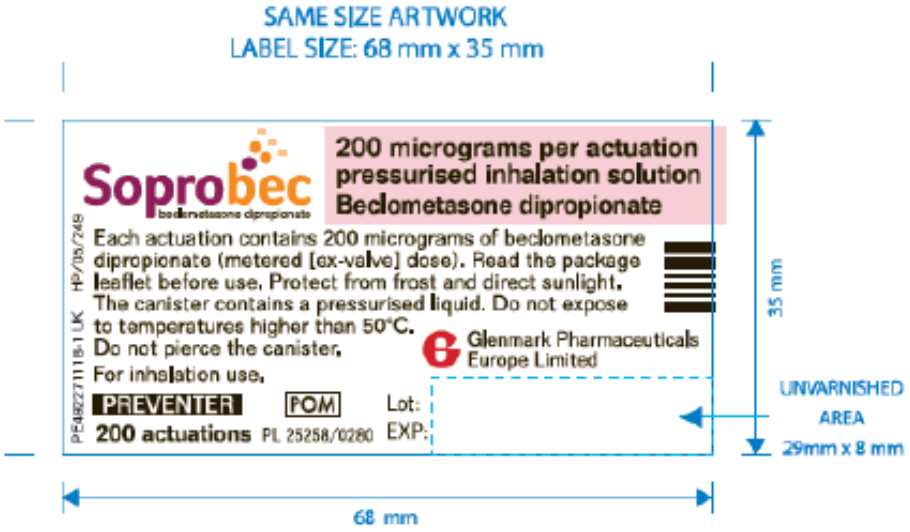
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Soprobec
beclometasone dipropionate
200 micrograms per actuation
pressurised inhalation solution
Beclometasone dipropionate
Each actuation contains 200 micrograms of beclometasone dipropionate (metered [ex-valve] dose). Read the package leaflet before use. Protect from frost and direct sunlight. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.
For inhalation use.
Glenmark Pharmaceuticals Europe Limited
PREVENTER
POM
Lot:
200 actuations
PL 25258/0280
EXP:
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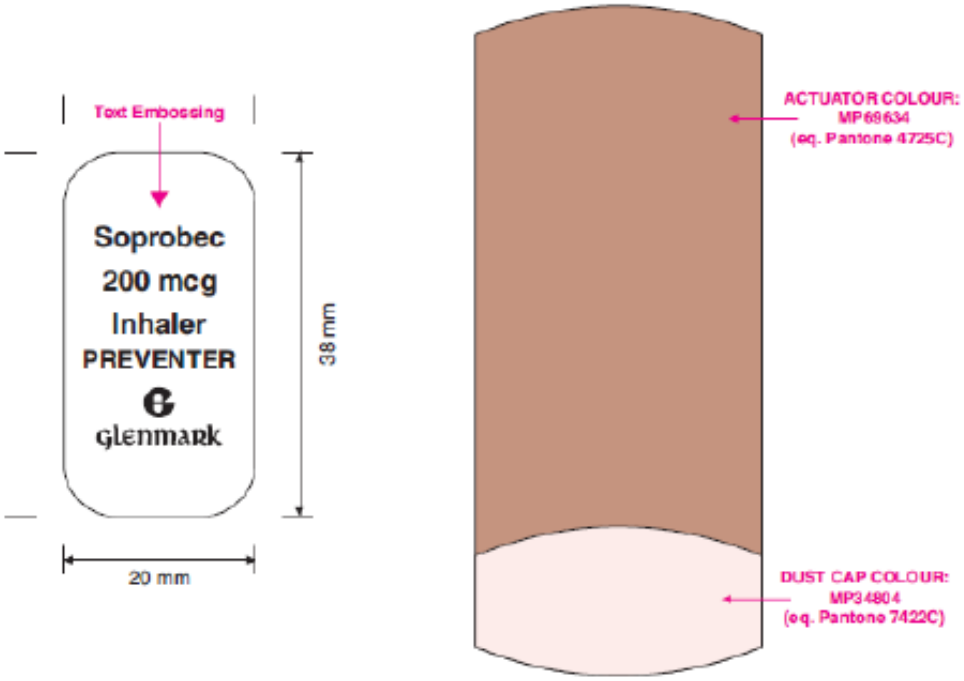
UNVARNISHED AREA
29mm x 8 mm
68 mm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200 mcg
Inhaler
PREVENTER
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20 mm
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DUST CAP COLOUR:
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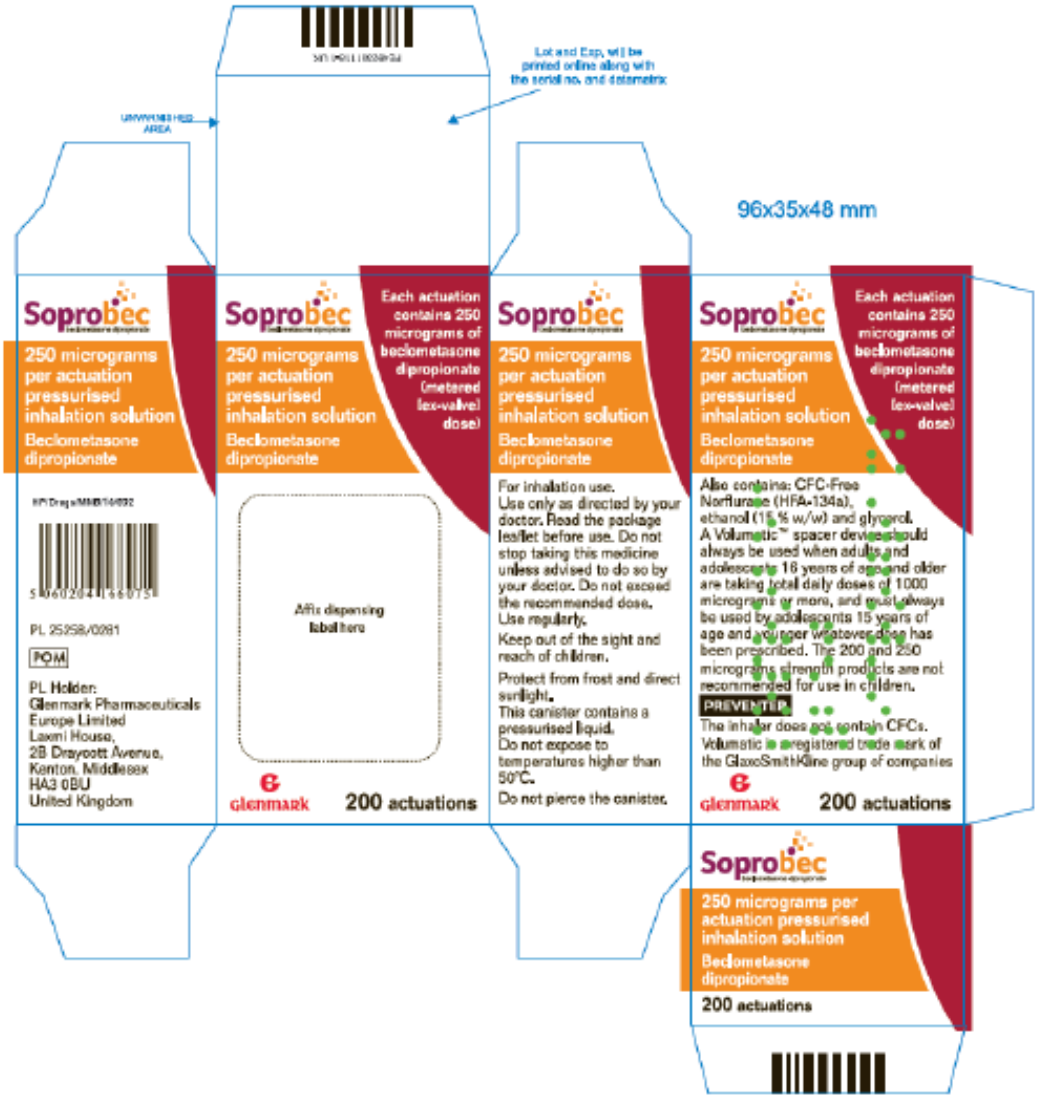
(eq. Pantone 7422C)



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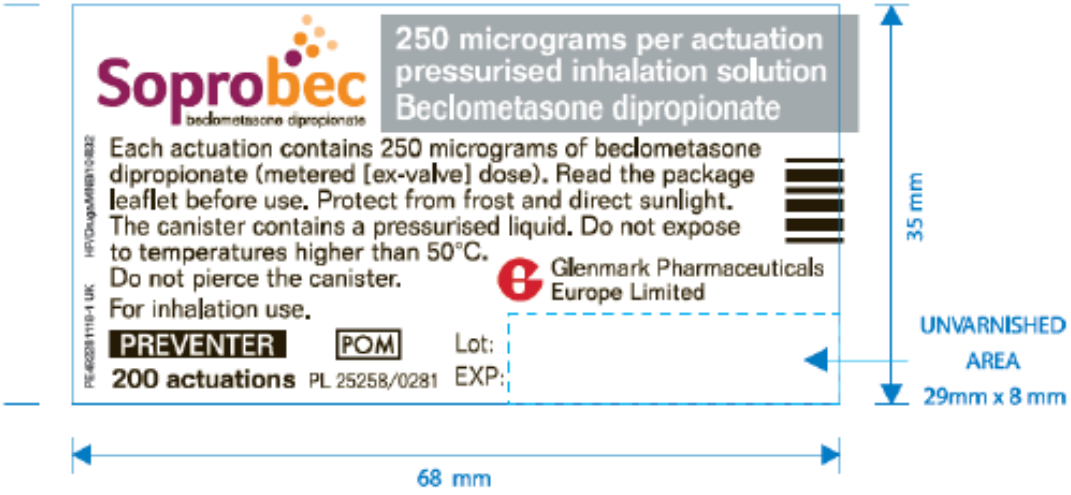

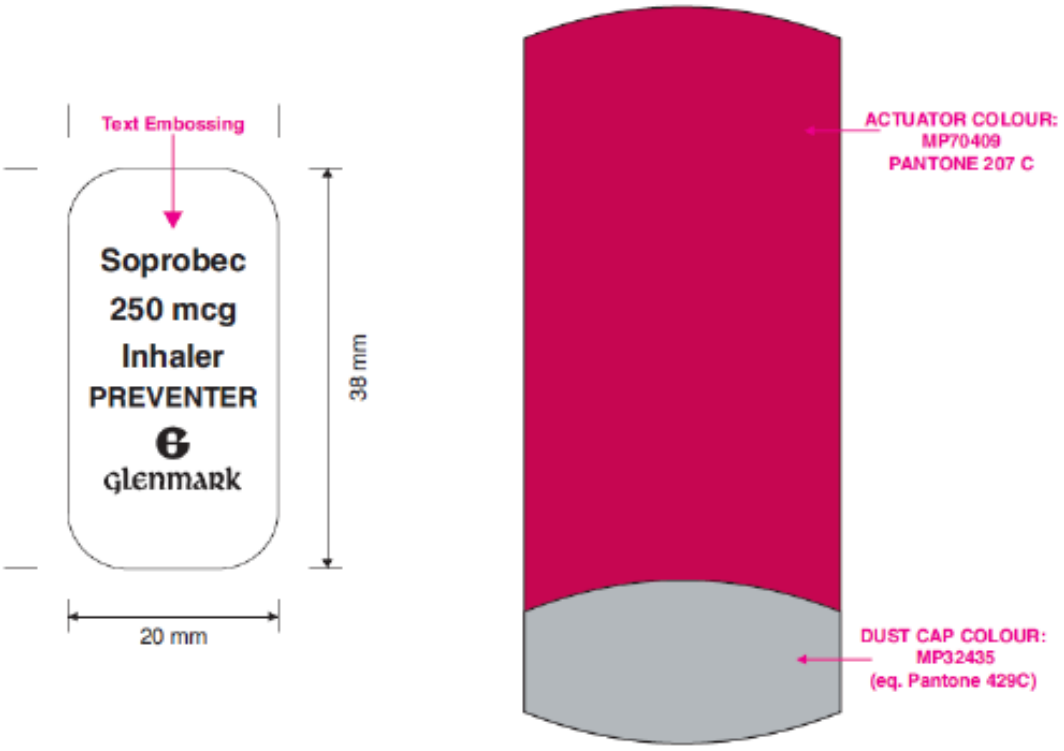

Annex 1

Table of content of the PAR update for MRP and DCP

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)