Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Flutiform K-haler 50 microgram/5 microgram per actuation pressurised inhalation, suspension
Flutiform K-haler 125 microgram/5 microgram per actuation pressurised inhalation, suspension

Affera K-haler 50 microgram/5 microgram per actuation pressurised inhalation, suspension
Affera K-haler 125 microgram/5 microgram per actuation pressurised inhalation, suspension

Abriff K-haler 50 microgram/5 microgram per actuation pressurised inhalation, suspension
Abriff K-haler 125 microgram/5 microgram per actuation pressurised inhalation, suspension

(Fluticasone propionate and formoterol fumarate dihydrate)

Procedure No: UK/H/2872 & 4378-4379/004-005/DC

UK Licence No: PL 16950/0338-0339 & 0350-0353

Napp Pharmaceuticals Limited.

LAY SUMMARY

Flutiform K-haler 50 microgram/5 microgram per actuation pressurised inhalation, suspension
Flutiform K-haler 125 microgram/5 microgram per actuation pressurised inhalation, suspension

Affera K-haler 50 microgram/5 microgram per actuation pressurised inhalation, suspension
Affera K-haler 125 microgram/5 microgram per actuation pressurised inhalation, suspension

Abriff K-haler 50 microgram/5 microgram per actuation pressurised inhalation, suspension
Abriff K-haler 125 microgram/5 microgram per actuation pressurised inhalation, suspension

(Fluticasone propionate and formoterol fumarate dihydrate)

This is a summary of the Public Assessment Report (PAR) for Flutiform K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0338-339; UK/H/2872/004-005/DC), Affera K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0350-0351; UK/H/4378/004-005/DC) and Abriff K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0352-0353; UK/H/4379/004-005/DC). It explains how Flutiform/Affera/Abriff K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension 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 Flutiform/Affera/Abriff K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension.

The products will be collectively referred to as Flutiform/Affera/Abriff K-haler throughout the remainder of this public assessment report (PAR).

For practical information about using Flutiform/Affera/Abriff K-haler, patients should read the package leaflet or contact their doctor or pharmacist.

What is and what is it used for?
Flutiform/Affera/Abriff K-haler is an inhaler (a pressurised inhalation suspension) which contains two active ingredients: fluticasone propionate and formoterol fumarate dihydrate. This medicine helps to prevent breathing problems such as asthma and helps to stop the patient becoming breathless and wheezy. However, it does not work if the patient is already having an asthma attack i.e. the patient is already breathless and wheezing. The patient will need to use a fast-acting 'reliever' medicine such as salbutamol if this happens.

How does Flutiform/Affera/Abriff K-haler work?
Fluticasone propionate belongs to a group of medicines called steroids. Steroids help to reduce swelling and inflammation in the lungs.
Formoterol fumarate dihydrate belongs to a group of medicines called long-acting beta$_2$ agonists. Long-acting beta$_2$ agonists are long-acting bronchodilators which help the airways in the lungs to stay open, making it easier for the patient to breathe.

Together these two active ingredients help to improve the patient's breathing. It is advised that the patient should use this medicine every day as directed by their doctor or asthma nurse. The inhaler is breath-triggered (or breath-actuated) which means that it will release these two active ingredients when the patient breathes in through the mouthpiece.

How is Flutiform/Affera/Abriff K-haler used?

The pharmaceutical form of Flutiform/Affera/Abriff K-haler is a pressurised inhalation, suspension and the route of administration is via inhalation through the mouth.

The patient should always use this inhaler exactly as their doctor, pharmacist or asthma nurse has told them. The patient should check with their doctor, or asthma nurse if they are not sure. The patient should use their inhaler regularly i.e. two actuations (puffs) in the morning and two actuations (puffs) in the evening every day to get the most benefit from their inhaler, unless their doctor tells them otherwise or advises them to stop. Do not take more than the prescribed dose. The patient's doctor may have prescribed their inhaler for a different indication other than asthma/or at a different dose from that normally prescribed and as described in the leaflet. The patient should always use their inhaler exactly as their doctor or asthma nurse has advised. If the patient is not sure about how much to take or how often to use their inhaler, they should check with their doctor, pharmacist or asthma nurse.

Adults and adolescents over 12 years of age

The usual dose is two inhalations twice a day, that is two puffs (actuations) in the morning and two in the evening. The patient's doctor or asthma nurse will prescribe the dose required to treat their asthma.

Flutiform/Affera/Abriff K-haler should not be used in children under 12 years of age.

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

The medicine can only be obtained with a prescription.

What benefits of Flutiform/Affera/Abriff K-haler have been shown in studies?

Flutiform/Affera/Abriff K-haler is a fixed combination product of known active substances. The company provided its own data on efficacy and safety studies. These studies have shown that Flutiform/Affera/Abriff K-haler helps to prevent breathing problems such as asthma and helps to stop the patient becoming breathless and wheezy.

What are the possible side effects of Flutiform/Affera/Abriff K-haler?

Like all medicines, this inhaler can cause side effects, although not everybody gets them. The patient's doctor or asthma nurse will prescribe the lowest dose necessary to control their asthma which may reduce the possibility of side effects occurring.

All medicines can cause allergic reactions, although serious allergic reactions are reported rarely. The patient should tell their doctor immediately if they get any sudden swelling of the eyelids, face, throat, tongue or lips, rash or itching especially those covering the whole body, symptoms such as dizziness, light-headedness or fainting or any sudden changes in their breathing pattern such as increased wheezing or shortness of breath.

As with other inhalers, the patient's breathing may worsen immediately after the patient uses their inhaler. They may notice an increase in wheezing and shortness of breath. If this happens the patient should stop using their Flutiform/Affera/Abriff K-haler and use their quick acting 'reliever' inhaler. The patient should contact their doctor or asthma nurse straight away. The patient's doctor or asthma nurse will assess them and may start the patient on a different course of treatment. The patient should carry their 'reliever' inhaler with them at all times.

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

For the full list of all side effects reported with Flutiform/Affera/Abriff K-haler, see section 4 of the package leaflet available on the MHRA website.

Why is Flutiform/Affera/Abriff K-haler approved?

The MHRA decided that Flutiform/Affera/Abriff K-haler's benefits are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Flutiform/Affera/Abriff K-haler?

A risk management plan (RMP) has been developed to ensure that Flutiform/Affera/Abriff K-haler is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Flutiform/Affera/Abriff K-haler 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 Flutiform/Affera/Abriff K-haler.

For Flutiform K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0338-339; UK/H/2872/004-005/DC):

Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Spain, Finland, Ireland, Iceland, Italy, Luxembourg, Norway, Portugal, Sweden, Slovak Republic and the UK agreed to grant Marketing Authorisations for Flutiform K-haler 50 and 125 microgram/5 microgram per actuation pressurised inhalation, suspension on 03 October 2017. Marketing Authorisations were granted in the UK on 01 November 2017.

For Affera K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0350-0351; UK/H/4378/004-005/DC):

Germany, Spain, Italy and UK agreed to grant Marketing Authorisations for Affera K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension on 03 October 2017. Marketing Authorisations were granted in the UK on 01 November 2017.

For Abriff K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0352-0353; UK/H/4379/004-005/DC):

Spain, Italy and the UK agreed to grant Marketing Authorisations for Abriff K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension on 03 October 2017. Marketing Authorisations were granted in the UK on 01 November 2017.

The full PAR for Flutiform/Affera/Abriff K-haler follows this summary.

For more information about treatment with Flutiform/Affera/Abriff K-haler read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Flutiform/Affera/Abriff K-haler (PL 16950/0338-0339 & 0350-0353; UK/H/2872 & 4378-4379/004-005/DC) could be approved. This fixed-dose combination of fluticasone propionate and formoterol fumarate is indicated in adults and adolescents aged 12 years and above for the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long -acting β_2 agonist) is appropriate:

- For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2 agonist.

Or

- For patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 agonist.

The products are prescription-only medicines

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and:

For Flutiform K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0338-339; UK/H/2872/004-005/DC):

Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Spain, Finland, Ireland, Iceland, Italy, Luxembourg, Norway, Portugal, Sweden and the Slovak Republic as concerned member states (CMS).

For Affera K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0350-0351; UK/H/4378/004-005/DC):

Germany, Spain and Italy as CMS.

For Abriff K-haler 50 microgram/5 microgram and 125 microgram/5 microgram per actuation pressurised inhalation, suspension (PL 16950/0352-0353; UK/H/4379/004-005/DC):

Spain and Italy as CMS.

The applications were submitted under Article 10(b) of Directive 2001/83/EC, as amended, applicable for a fixed combination product of known active substances.

Flutiform/Affera/Abriff K-haler pressurised inhalation, suspension is a new presentation of the authorised combination product Flutiform pressurised inhalation, suspension. Both products contain the same formulation of fluticasone propionate and formoterol fumarate in a hydrofluoralkane (HFA) propellant administered by a metered dose inhaler. However, whereas the existing product is delivered via a traditional press-and-breathe (P&B) device, the Flutiform/Affera/Abriff K-haler product is a breath-actuated inhaler (BAI).

Napp Pharmaceuticals Limited has submitted one Complex and one Standard Abridged Marketing Authorisation Applications for Flutiform K-haler haler 50/5 micrograms and 125/5micrograms Pressurised inhalation suspension, through the Decentralised Procedure for Human Medicinal Products and seeks Marketing Authorisations as line extension to the original Flutiform Press and Breathe (P&B) inhalers in the CMS.

The Applicant has also submitted two sets of two duplicate Standard Abridged Marketing Authorisation Applications, for Affera K-haler and Abriff K-haler 50/5 & 125/5 micrograms pressurised inhalation, suspension, through the Decentralised Procedure seeking Marketing Authorisations as line extensions to the original Flutiform Press and Breathe (P&B) inhalers in the CMS.

The original Decentralised Procedures for the Flutiform inhalers included a Paediatric Investigation Plan (PIP) – PIP Decision Number(s): EMEA-00127-PIP01-07 [EMEA/PDCO/57037/2009] – which has undergone compliance verification– PDCO Compliance Opinion Number: EMEA-CI-000127-PIP01-07.

The Applicant has submitted a PIP amendment to the original PIP on 16 December 2014 in accordance to Article 7 of the Paediatric Regulation. PIP Decision Number is EMEA-000127-PIP01-07-M03 which has undergone PIP compliance verification: EMEA-C-000127-PIP01-07-M03. The PIP decision confirms that a waiver has been accepted for assessment of the inhaler in children less than 5 years old with asthma and deferral has been issued for the conduct of the proposed clinical studies in the paediatric population less than 12 years of age with Flutiform and associated names, has been granted.

Fluticasone propionate and formoterol fumarate represent two classes of medications; a synthetic corticosteroid and a selective, long-acting β2-adrenergic receptor agonist respectively, and as with other inhaled corticosteroid and long-acting β2- adrenergic receptor agonist combinations additive effects are seen in terms of reduction of asthma exacerbations.
Pharmacotheropeutic Group: - Adrenergics in combination with corticosteroids or other drugs excl. anticholinergics:
ATC code: R03AK11 – Formoterol and fluticasone.

Traditional pressurised metered dose inhalers have been considered to be a cost-effective drug delivery mechanism to deliver drugs targeted to the lungs. However, as the effective drug delivery is reliant on the patient correctly co-ordinating the release of the dose from the pressurised canister with the inhalation manoeuvre, the 'press-and-breathe' devices have been linked to compliance issues as a result of poor patient co-ordination. Incorrect handling of the device may lead to patients not getting the correct dose, and thereby in turn compromising disease control.

The introduction of this new product will offer patients the same important benefits as the existing Flutiform i.e. the anti-inflammatory effects and asthma control provided by fluticasone propionate with the rapid long-lasting bronchodilation provided by formoterol fumarate, with the added benefit of a simpler to operate administration device.

The clinical development programme for these line extension applications consisted of three studies (a charcoal block validation and pharmacokinetic study, a systemic exposure and pharmacodynamic study and a device handling study) comparing the higher strength (125/5 microgram) of this fixed-dose combination (FDC) administered via the breath-actuated inhaler (BAI) with the same strength of this FDC administered via the pressurised metered dose inhaler (pMDI) both without and with the AeroChamber Plus spacing device. In addition the ability of patients to trigger the BAI was evaluated in a handling study.

The grant of the original Marketing Authorisations for the Flutiform inhalers allowed use of the pMDI without a spacing device and together with the AeroChamber Plus spacing device. The Applicant has stated that the studies were conducted in accordance with Good Clinical Practice (GCP) guidelines. The outcomes from the three studies presented are intended to supplement the existing Flutiform inhaler dossier which includes a total of 18 studies. Six of these were pharmacokinetic studies including pharmacodynamics assessments in two studies, one pharmacodynamic study, two phase II efficacy and safety studies and nine Phase III studies including data from five pivotal Phase III studies.

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.

The RMS and CMS considered that the application could be approved at the end of procedure on 03 October 2017. After a subsequent national phase, a licence was granted in the UK on 01 November 2017.

II QUALITY ASPECTS

II.1 Introduction

For Flutiform/Affera/Abriff K-haler 50 microgram/5 microgram per actuation pressurised inhalation, suspension:
Each metered dose (ex-valve) contains:
50 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 46 micrograms of fluticasone propionate and 4.5 micrograms of formoterol fumarate dihydrate.

Flutiform/Affera/Abriff K-haler 125 microgram/5 microgram per actuation pressurised inhalation, suspension:
Each metered dose (ex-valve) contains:
125 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 115 micrograms of fluticasone propionate and 4.5 micrograms of formoterol fumarate dihydrate.

Other ingredients consist of the following pharmaceutical excipients sodium cromoglicate, ethanol anhydrous and apaflurane HFA 227.

The breath-triggered actuator is pale grey with an integrated dose indicator and an orange mouthpiece cover. The suspension is contained in an aluminium pressurised container crimped with a standard metering valve. This canister is sealed inside the breath-triggered actuator fitted with a mouthpiece cover (both made of polypropylene) and an integrated dose indicator which indicates the number of actuations remaining. Each container delivers 120 actuations. The assembled inhaler is pouched in an aluminium foil laminate and is packed in a cardboard carton.

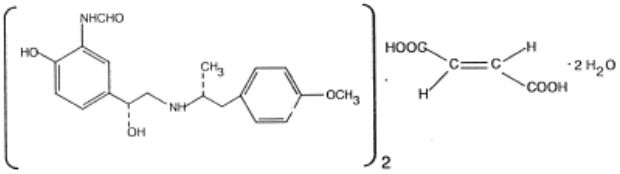
Flutiform/Affera/Abriff K-haler is available in pack sizes of 1 inhaler (120 actuations) and a multipack of 3 x 1 inhaler (120 actuations). Not all pack sizes may be marketed.

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

II.2. Drug Substances

(1) Formoterol fumarate dihydrate

INN: Formoterol fumarate (dihydrate)
Chemical name: N-[2-hydroxy-5-[1(RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (E)-butenedioate dihydrate
Structure:



Molecular formula: $C_{42}H_{52}N_4O_{12}.2H_2O$
Molecular weight: 840.9g/mol
Appearance: A white to off white or slightly yellow powder.
Solubility: Soluble in methanol, slightly soluble in water and 2-propranol and practically insoluble in acetonitrile.

Formoterol fumarate dihydrate is the subject of a European Pharmacopoeia monograph.

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

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

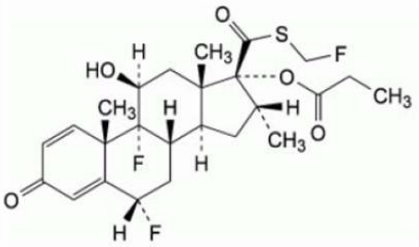
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

(2) Fluticasone propionate

INN: Fluticasone propionate

Structure:



Molecular formula: $C_{25}H_{31}F_3O_5S$

Molecular weight: 500.6g/mol

Appearance: White to almost white powder.

Solubility: It is practically insoluble in water, sparingly soluble in dichloromethan and slightly soluble in ethanol.

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 (EDQM) Certificate of Suitability.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to devise a new presentation of the authorised combination product Flutiform pressurised inhalation, suspension. Both products contain the same formulation of fluticasone propionate and formoterol fumarate in a hydrofluoralkane (HFA) propellant administered by a metered dose inhaler. However, whereas the existing product is delivered via a traditional press-and-breathe (P&B) device, Flutiform/Affera/Abriff K-haler product incorporates a breath-actuated inhaler (BAI).

A satisfactory account of the pharmaceutical development has been provided.

In accordance with the requirements of the EMEA Guideline on Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005, corr.) formulation development studies were conducted which justified the necessity of the materials for use as excipients in the proposed formulation. The development of the product is sufficiently described in accordance with EMEA/CHMP/QWP/49313/2005 Corr.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of sodium cromoglicate and ethanol anhydrous which are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

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

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. 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 for the unopened product with the storage conditions ‘Do not store above 25°C. Do not refrigerate or freeze. If the inhaler is exposed to freezing conditions then the patient must be advised

to allow the inhaler to warm at room temperature for 30 minutes then actuate the inhaler once before use.
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn, even when apparently empty.'

The in-use shelf life of the inhaler is 3 months after opening the foil pouch.

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
Flutiform Breath-Actuated Inhaler (BAI) is a new presentation of the authorised combination product Flutiform pressurised inhalation, suspension. Since Flutiform BAI shares the same formulation, manufacturing process, bulk canister and metering valve as the currently registered Flutiform P&B no additional non-clinical testing has been conducted with the BAI. This approach is acceptable as generic applications referring to dossiers based on combination dossiers are in accordance with EC Notice to Applicants, Volume 2A, Chapter 1 as all relevant information is in the dossier of the original medicinal product.

The pharmacodynamic, pharmacokinetic and toxicological properties of fluticasone propionate and formoterol fumarate are well known and therefore further studies are not required. Overview based on literature review is, thus, appropriate.

The MAH'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 Toxicology
Drug Product
The excipients in the proposed formulation are HFA 227, ethanol and sodium cromoglicate, which are well-known and used in inhalation medicinal products. There are therefore no safety concerns as a result of their inclusion in the proposed product.

Impurities and residual solvents
All but one impurity was toxicologically qualified and the levels of the additional impurity (formoterol fumurate ethanolic derivative) were below the ICH Q3B (R2) thresholds for identification and qualification (1.0% or 5 µg/day). None of the drug-related impurities were considered to represent a safety issue for patients.

Extractables and leachables
As the same formulation, manufacturing process, and bulk canister and metering valve are the same between the Flutiform P&B and BAI products, the evaluation of extractables, leachables and impurities remain valid for this application for Flutiform BAI.

Given that the drug product will come into contact with the polypropylene of the K-valve within the BAI device, the Applicant has conducted a safety assessment on the extractables and leachables from the K-valve material. The NOAELs, TIs, TEs and PDEs were derived for each of the extractable and leachables identified from the K-valve material used in the Flutiform Breath Activated Inhaler (BAI). The PDEs have been calculated using the recommendations outlined in ICH guidance Q3C(R5), which is acceptable. The calculated levels and potential exposure to the extractables/leachables from the K-valve material are considerably lower than the PDE limits, TIs and TEs and are therefore unlikely to be a cause for concern for human safety.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Flutiform BAI is intended to be used in the same target population(s) as currently registered for Flutiform P&B, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

However, an environmental risk assessment for Flutiform BAI has been submitted based on the environmental risk assessment for Flutiform P&B, which is acceptable.

The LogP values of FP and FF are stated as 3.46 and 0.4, respectively. No additional investigation into persistence, bioaccumulation or toxicity is required in line with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) as these are below the threshold value of 4.5.

$PEC_{surfacewater}$ values of 2.5×10^{-6} mg/L and 1×10^{-7} mg/L have been calculated for FP and FF respectively using $DOSE_{ai}$ values of 0.5 (FP) and 0.02 (FF) and the default values for F_{pen}, WasteWinhab and Dilution. No Phase II assessment is required in line with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). The $PEC_{surfacewater}$ values are below the threshold that triggers a Phase II assessment.

The Applicant has also provided evidence to show that Flutiform BAI is intended to be used in the same target population(s) as currently registered for Flutiform P&B and that the sales of fluticasone proprionate have declined slightly in the UK, France, Germany, Italy and Spain. As a result, it is deemed that an acceptable ERA has been submitted for FP and FF and that there is no additional risk to the environment on licensing of this product.

III.6 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 applicant seeks authorisation for line extension applications for the first breath activated inhaler (BAI) delivering the same active ingredients as in the currently authorised Flutiform inhalers, fluticasone propionate and formoterol fumarate dihydrate, in fixed doses of 50/5 microgram and 125/5 microgram pressurised inhalation, suspension, with product names of Flutiform, Affera and Abriff K-haler 50/5 microgram and 125/5 microgram pressurised inhalation, suspension. These fixed-dose combination BAIs contain the same propellant as the currently authorised Flutiform inhaler i.e. the hydrofluoroalkane (HFA) propellant (Apaflurane HFA 227), a non-chlorofluorocarbon (CFC) alternative propellant. Other excipients include alcohol (ethanol, anhydrous) as a wetting agent and sodium cromoglicate as a suspension aid and moisture scavenger.

The BAI allows inhalation without the need for synchronisation of inhalation with actuation of the pressurised metered dose inhaler without spacing device.

The information in the dossier in support of Marketing Authorisations for these collections of BAIs includes pharmacokinetic and pharmacodynamic data comparing the higher strength (125/5 microgram) of this FDC administered via the BAI with the same strength of this FDC administered via the pMDI both without and with the AeroChamber Plus spacing device. In addition the ability of patients to trigger the BAI was evaluated in a handling study. The grant of the original Marketing Authorisations for the Flutiform inhalers allowed use of the pMDI without a spacing device and together with the AeroChamber Plus spacing device.

The outcomes from the three studies presented are intended to supplement the existing Flutiform inhaler dossier which includes a total of 18 studies. Six of these were pharmacokinetic studies including pharmacodynamics assessments in two studies, one pharmacodynamic study, two phase II efficacy and safety studies and nine Phase III studies including data from five pivotal Phase III studies.

The three studies submitted by the applicant in support of these applications are summarised and tabulated as follows:

- Protocol KFL 1501 is a charcoal block validation study and a pharmacokinetic study.
- Protocol KFL 1503 is a systemic exposure study and pharmacodynamic assessment
- Protocol KFL 9501 is a device handling study in patients using the BAI and comparing this with the pMDI without a spacing device, both inhalers containing placebo:

Study ID **Location**	**Objective** **Population** **Age**	**Design**	**Treatments**
Single dose			
KFL1501	Compare pulmonary drug exposure with Flutiform BAI, pMDI and pMDI +/- spacer Healthy volunteers ≥ 18 years	Stage 1: Charcoal block validation Open label, single dose, 4-period, crossover study	Stage 1 Oral Formoterol capsule 2 x 12 µg, single dose +/- oral charcoal
		Stage 2: Pulmonary PK study Randomised, open-label, 3-way crossover, single-dose study	Stage 2 Oral charcoal + single inhaled dose: • pMDI 125/5 µg x 2 puffs • pMDI +spacer 125/5 µg x 2 puffs • BAI 125/5 µg x 2 puffs
KFL1503	Compare systemic drug exposure and pharmacodynamic effects with Flutiform BAI and pMDI +/- spacer Healthy volunteers ≥ 18 years	Group 1: Systemic PK study Randomised, open-label, 3-way crossover, single-dose study	Group 1 Single inhaled dose: • Flutiform pMDI 125/5 µg x 2 puffs • Flutiform pMDI + spacer 125/5 µg x 2 puffs • Flutiform BAI 125/5 µg x 2 puffs
		Group 2: Safety PD study Randomised, open-label, 5-way crossover, supratherapeutic single – dose	Group 2 Single inhaled dose: • Flutiform pMDI 125/5 µg x 12 puffs • Flutiform pMDI + spacer 125/5 µg x 12 puffs • Flutiform BAI 125/5 µg x 12 puffs • Flutiform pMDI 125/5 µg x 4 puffs • Atimos Modulite pMDI 12 µg x 5 puffs
KFL9501	Assess whether subjects can correctly use BAI and pMDI, and trigger BAI to fire Asthma & COPD ≥ 12 years	Randomised, open-label, 2-way crossover, handling study	Inhaled, single dose without spacer: • Flutiform pMDI • Flutiform BAI • Placebo

PK = pharmacokinetics, PD = pharmacodynamics

STUDY KLF 1501
Charcoal Block Validation Phase

The charcoal block validation was conducted to determine an activated charcoal dose and schedule of administration to block gastrointestinal absorption of orally administered formoterol fumarate. The validated dosing regimen was then used to study pulmonary exposure of formoterol fumarate delivered via the BAI 125/5 and via the pMDI 125/5 both without and with spacing device following administration of charcoal.

Four alternative charcoal block regimens were evaluated in the charcoal block validation phase of Study KFL1501. This phase of the study consisted of 5 periods; subjects received a single dose of oral formoterol (2 x 12 µg capsules) on Day 1 of each study period, during the subsequent periods subjects received oral formoterol (2 x 12 µg capsules) and a charcoal block regimen. Each study period was separated by a 7 day washout period.

All charcoal block regimens that were tested provided near-complete blockade of formoterol absorption from the GI tract. The charcoal dosing regimen ultimately selected to be used in the Main Stage of the study was regimen D: activated charcoal administered 10 g pre-dose, 10 g 15 minutes post-dose and 10 g at 1 hour post-dose. This regimen showed complete blockade of oral formoterol absorption in all patients. The delayed second administration (15 minutes post-dose) was deemed optimal to minimise interference with the intensive post-dose PK sampling required following inhaled formoterol administration.

IV.2 Pharmacokinetic studies

STUDIES KFL 1501 and KFL 1503:
The study designs to evaluate the pharmacokinetic profile of the FDC of fluticasone propionate and formoterol fumarate 125/5micrograms administered via the BAI compared with the same FDC administered via a pMDI without spacing device and with a spacing device were similar for both pulmonary deposition and systemic bioavailability (see summary table above). The test and reference products used in the studies were:

	Test	**Reference**
Product name	Fluticasone propionate/ Formoterol fumarate BAI *without spacer*	Fluticasone propionate/ Formoterol fumarate (Flutiform®) pMDI *with and without spacer*
Unit Strength	125/5 µg	125/5 µg
Dosage form	Pressurised metered dose inhalation, suspension	Pressurised metered dose inhalation, suspension
Dose and route	2 puffs of 125/5 µg	2 puffs of 125/5 µg

The two pharmacokinetic studies (refer to summary Table) were conducted following overnight fasting conditions with a standard dietary menu during the day.

In the two studies, blood samples for measurement of fluticasone propionate and formoterol fumarate plasma levels were collected pre-dose and up to and including 36 hours after each administration.

The results of the pharmacokinetic studies (KFL 1501: pulmonary pharmacokinetic study and KFL 1503: systemic pharmacokinetic study) are presented below.

Table: Relative bioavailability of fluticasone propionate for study KFL 1501 (pulmonary pharmacokinetic):

Parameter	Treatment Group	LS Geometric Mean	LS Geometric Mean 90% CI	Ratio (%) (Test/Reference)	Confidence Level (CL)	CL% Confidence Interval
AUCt (pg.h/mL)	BAI	274.52	(244.25, 308.54)	117.16	94.12	(96.81, 141.79)
	pMDI *	234.32	(208.48, 263.35)			
	BAI	274.71	(250.65, 301.09)	80.52	90	(70.73, 91.67)
	pMDI +S *	341.15	(311.27, 373.91)			
	pMDI +S	346.00	(318.03, 376.42)	146.49	90	(130.03, 165.04)
	pMDI *	236.18	(217.09, 256.95)			
AUCINF (pg.h/mL)	BAI	329.73	(294.11, 369.67)	117.05	90	(99.58, 137.59)
	pMDI *	281.69	(251.26, 315.82)			
	BAI	327.44	(298.32, 359.41)	84.24	90	(73.84, 96.10)
	pMDI +S *	388.72	(354.15, 426.67)			
	pMDI +S	404.33	(369.03, 443.00)	144.98	90	(127.41, 164.97)
	pMDI *	278.89	(254.55, 305.57)			

Parameter	Treatment Group	LS Geometric Mean	LS Geometric Mean 90% CI	Ratio (%) (Test/Reference)	Confidence Level (CL)	CL% Confidence Interval
Cmax (pg/mL)	BAI	25.39	(23.30, 27.66)	106.96	94.12	(92.97, 123.04)
	pMDI *	23.74	(21.78, 25.86)			
	BAI	25.29	(23.47, 27.26)	83.69	90	(75.30, 93.02)
	pMDI +S *	30.22	(28.05, 32.57)			
	pMDI +S	30.69	(28.63, 32.90)	127.92	90	(115.94, 141.13)
	pMDI *	23.99	(22.36, 25.72)			

BAI= Fluticasone/Formoterol BAI, pMDI= Flutiform pMDI without Spacer, pMDI +S=Flutiform pMDI with Spacer.
PK parameters were analysed using ANOVA with fixed terms for treatment, period, planned sequence and subject within sequence. The ratio was calculated by transforming the difference between the natural log LS Means back to the linear scale.
* Reference treatment for this comparison.
Statistical analysis was performed on n subjects restricted to those with data for both BAI and reference treatments in the PK analysis set and additionally for AUCINF with corresponding R^2 values >= 0.85.

Table: Relative bioavailability of fluticasone propionate for study KFL 1503 (systemic pharmacokinetic):

Parameter	Treatment Group	Exp (LS Mean)	Exp (LS Mean) 90% CI	Ratio (%) (Test/ Reference)	Confidence Level (CL)	CL% Confidence Interval
PRIMARY COMPARISON						
AUCt (pg.h/mL)	BAI	198.03	(176.70, 221.93)	75.93	94.12	(63.06, 91.43)
	pMDI+S*	260.81	(232.72, 292.29)			
Cmax (pg/mL)	BAI	17.65	(16.23, 19.19)	76.00	94.12	(66.31, 87.09)
	pMDI+S*	23.22	(21.36, 25.25)			
AUCINF (pg.h/mL)	BAI	251.96	(224.75, 282.47)	76.24	90	(64.88, 89.59)
	pMDI+S*	330.48	(294.79, 370.49)			
SECONDARY COMPARISONS						
AUCt (pg.h/mL)	BAI	194.50	(171.64, 220.42)	116.93	90	(98.15, 139.30)
	pMDI *	166.34	(146.78, 188.50)			
Cmax (pg/mL)	BAI	16.96	(15.54, 18.52)	104.72	90	(92.62, 118.41)
	pMDI *	16.20	(14.84, 17.68)			
AUCINF (pg.h/mL)	BAI	242.51	(212.54, 276.69)	117.74	90	(97.97, 141.50)
	pMDI *	205.96	(180.51, 235.00)			
AUCt (pg.h/mL)	pMDI+S	262.14	(231.91, 296.32)	148.57	90	(125.02, 176.56)
	pMDI *	176.44	(156.09, 199.44)			
Cmax (pg/mL)	pMDI+S	22.88	(21.15, 24.75)	135.65	90	(121.44, 151.51)
	pMDI *	16.87	(15.60, 18.25)			
AUCINF (pg.h/mL)	pMDI+S	356.07	(315.00, 402.50)	145.42	90	(122.46, 172.68)
	pMDI *	244.86	(216.61, 276.79)			

BAI = Fluticasone/Formoterol BAI, pMDI = Flutiform pMDI without Spacer, pMDI+S = Flutiform pMDI with Spacer.
Log transformed PK parameters were analysed using ANOVA with fixed terms for treatment, period, planned sequence and subject within sequence. The ratio was calculated by transforming the difference between the natural log LS Means back to the original scale.
* For each comparison, this is considered as the reference arm

Table: Fluticasone propionate AUC% extrapolation observed (KFL 1501 & 1503 study pulmonary pharmacokinetic)

Treatment groups	KFL 1501	KFL 1503
	AUC_{0-t} <80% $AUC_{0-\infty}$ %	AUC_{0-t} <80% $AUC_{0-\infty}$ %
BAI	8.7	16.3
pMDI with spacing device	9.1	13.6
pMDI without spacing device	16.3	**26.8**

Table: Relative bioavailability of formoterol fumarate for study KFL 1501 (pulmonary pharmacokinetic):

Parameter	Treatment Group	LS Geometric Mean	LS Geometric Mean 90% CI	Ratio (%) (Test/Reference)	Confidence Level (CL)	CL% Confidence Interval
AUCt (pg.h/mL)	BAI	23.72	(20.27, 27.76)	130.51	94.12	(100.94, 168.74)
	pMDI *	18.18	(15.53, 21.27)			
	BAI	23.26	(20.38, 26.54)	101.74	90	(84.41, 122.63)
	pMDI +S *	22.86	(20.03, 26.09)			
	pMDI +S	23.49	(21.11, 26.15)	129.14	90	(110.99, 150.26)
	pMDI *	18.19	(16.34, 20.25)			
AUCINF (pg.h/mL)	BAI	30.97	(26.80, 35.80)	137.61	90	(112.12, 168.90)
	pMDI *	22.51	(19.47, 26.02)			
	BAI	33.19	(30.36, 36.28)	116.14	90	(102.39, 131.74)
	pMDI +S *	28.57	(26.14, 31.24)			
	pMDI +S	30.53	(27.57, 33.80)	131.84	90	(114.14, 152.28)
	pMDI *	23.16	(20.91, 25.64)			

KFL1501

Parameter	Treatment Group	LS Geometric Mean	LS Geometric Mean 90% CI	Ratio (%) (Test/Reference)	Confidence Level (CL)	CL% Confidence Interval
Cmax (pg/mL)	BAI	7.92	(7.13, 8.78)	128.96	94.12	(108.81, 152.85)
	pMDI *	6.14	(5.53, 6.81)			
	BAI	7.88	(7.19, 8.63)	95.07	90	(83.59, 108.13)
	pMDI +S *	8.29	(7.56, 9.07)			
	pMDI +S	8.38	(7.72, 9.09)	135.47	90	(120.71, 152.04)
	pMDI *	6.18	(5.70, 6.71)			

Cross-reference: Listing 16.2.4.2 and Table 14.4.6.1.
N: Number of subjects in population. n: Number of subjects with data available (for both test and reference treatments).
BAI= Fluticasone/Formoterol BAI, pMDI= Flutiform pMDI without Spacer, pMDI +S=Flutiform pMDI with Spacer.
PK parameters were analysed using ANOVA with fixed terms for treatment, period, planned sequence and subject within sequence. The ratio was calculated by transforming the difference between the natural log LS Means back to the linear scale.
* Reference treatment for this comparison. Statistical analysis was performed on n subjects restricted to those with data for both BAI and reference treatments in the PK analysis set and additionally for AUCINF with corresponding R^2 values >= 0.85.

Table: Relative bioavailability of formoterol fumarate for study KFL 1503 (systemic pharmacokinetic):

Parameter	Treatment Group	Exp (LS Mean)	Exp (LS Mean) 90% CI	Ratio (%) (Test/ Reference)	Confidence Level (CL)	CL% Confidence Interval
PRIMARY COMPARISON						
AUCt (pg.h/mL)	BAI	32.40	(29.83, 35.20)	108.58	94.12	(94.97, 124.13)
	pMDI*	29.84	(27.47, 32.42)			
Cmax (pg/mL)	BAI	5.71	(5.17, 6.32)	107.09	94.12	(91.04, 125.97)
	pMDI*	5.33	(4.83, 5.90)			
AUCINF (pg.h/mL)	BAI	40.18	(36.96, 43.68)	104.16	90	(93.06, 116.59)
	pMDI*	38.57	(35.48, 41.93)			
SECONDARY COMPARISONS						
AUCt (pg.h/mL)	BAI	34.35	(31.06, 37.99)	175.49	90	(152.24, 202.29)
	pMDI+S*	19.57	(17.70, 21.65)			
Cmax (pg/mL)	BAI	6.07	(5.42, 6.79)	101.32	90	(86.44, 118.77)
	pMDI+S*	5.99	(5.35, 6.70)			
AUCINF (pg.h/mL)	BAI	39.05	(35.59, 42.84)	163.68	90	(143.69, 186.44)
	pMDI+S*	23.86	(21.75, 26.18)			
AUCt (pg.h/mL)	pMDI+S	19.60	(18.12, 21.20)	62.87	90	(56.28, 70.23)
	pMDI*	31.17	(28.82, 33.72)			
Cmax (pg/mL)	pMDI+S	6.00	(5.44, 6.61)	106.78	90	(93.14, 122.42)
	pMDI*	5.62	(5.10, 6.19)			
AUCINF (pg.h/mL)	pMDI+S	25.44	(23.56, 27.48)	67.08	90	(60.19, 74.76)
	pMDI*	37.93	(35.13, 40.96)			

BAI = Fluticasone/Formoterol BAI, pMDI = Flutiform pMDI without Spacer, pMDI+S = Flutiform pMDI with Spacer.
Log transformed PK parameters were analysed using ANOVA with fixed terms for treatment, period, planned sequence and subject within sequence. The ratio was calculated by transforming the difference between the natural log LS Means back to the original scale.
*For each comparison, this is considered as the reference arm

Table: Formoterol fumarate AUC % extrapolation observed (KFL 1501 & 1503: Pulmonary & Systemic pharmacokinetic):

Treatment groups	**KFL 1501**	**KFL 1503**
	AUC_{0-t} <80% $AUC_{0-\infty}$ %	AUC_{0-t} <80% $AUC_{0-\infty}$ %
BAI	**25.0**	12.2
pMDI with spacing device	**32.6**	**27.9**
pMDI without spacing device	**39.0**	17.9

Pharmacokinetic conclusion

Fluticasone propionate

In the pulmonary pharmacokinetic study, fluticasone propionate exposure from the BAI was intermediate between that from the pMDI without and with a spacing device as observed from geometric means of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. A similar trend was observed in these pharmacokinetic parameters in the systemic bioavailability pharmacokinetic study.

The study results confirm the hypothesis for the pulmonary deposition study (KFL 1501) that the BAI was to achieve at least 80% of the exposure of fluticasone propionate observed with the pMDI without spacing device. Hence confirmation of this hypothesis is supportive of bridging the efficacy of fluticasone propionate delivered via the BAI with that of the pMDI without spacing device.

The upper limit of the 90% confidence interval (CI) was greater than 125% in the pulmonary [BAI/ pMDI without spacing device comparisons: CI>125% (AUC_{0-t}:141.79 and $AUC_{0-\infty}$:137.59)] and in the systemic pharmacokinetic [BAI/ pMDI without spacing device comparisons: CI>125% (AUC_{0-t}:139.30 and $AUC_{0-\infty}$:141.50] studies. However, safety has been demonstrated by reference to the pharmacokinetic comparisons between the K-Haler and the pMDI fitted with the spacing device. For fluticasone, the upper limit of the confidence interval of AUC_t and C_{max} for the ratio of BAI to pMDI + spacer is below 125% in both the pulmonary and systemic PK studies. The lower limit of the confidence interval is below 80% in each case. Overall, studies KFL1501 and KFL1503 show pulmonary and systemic bioavailability of fluticasone with BAI to be intermediate to that for pMDI without spacer and pMDI with spacer. To complement this data, the Applicant has provided in their responses to CMS comments a summary of safety data from the Flutiform clinical development programme relating to the use of the pMDI with a spacing device. These data are considered to adequately demonstrate the safety of Flutiform pMDI with spacer, and hence of the BAI, with respect to fluticasone.

In both KFL1501 and KFL1503, AUC_t was <80% AUC_{INF} for more than 20% of subjects in some study arms. The Applicant has provided a discussion of this in their response to RMS comments. In both studies, the study design generally appeared appropriate although a longer sampling period in KFL1503 may have allowed AUC_t to be determined at >80% AUC_{INF} in a greater number of subjects. Any concerns regarding study design are further alleviated as the analyses presented demonstrate that analysis of the subsets of patients with AUC_t > 80% AUC_{INF} for both components does not raise any concern, with the BAI/pMDI ratio exceeding the lower bioequivalence limit in KFL1501 and showing no evidence that analysis of the whole study population underestimates systemic exposure in KFL1503.

Formoterol fumarate

In the pulmonary pharmacokinetic study (KFL 1501), the geometric mean for AUC_{0-t} for formoterol fumarate administered via the BAI (23.32) was greater than that for formoterol fumarate administered via the pMDI without spacing (18.01) and with spacing device (22.67). Similarly, $AUC_{0-\infty}$ was greater for formoterol fumarate from the BAI (30.66) than from the pMDI without spacing device (22.65) and with spacing device (28.29). C_{max} was comparable following administration from the BAI and the pMDI without spacing device but was higher in the pMDI with spacing device treatment group. Mean T_{max} was comparable following administration from the BAI and the pMDI without spacing device, but was shorter in the pMDI with spacing device treatment group indicating faster drug delivery from the BAI. A similar trend was observed in the geometric mean values in the systemic pharmacokinetic study (KFL 1503).

The upper limit of the 90% confidence interval was >125% in the pulmonary pharmacokinetic study, when formoterol fumarate expsoure was compared between BAI and the pMDI without spacing device – AUC_{0-t}:168.74; $AUC_{0-\infty}$ 168.90 and C_{max} 152.85.

In the systemic pharmacokinetic study, secondary comparisons of AUC for formoterol fumarate showed that both the lower and upper limit of the CI on comparisons between BAI and the pMDI with spacing device exceeded 125% - AUC_{0-t} 152.24, 202.29 and $AUC_{0-\infty}$ 143.69, 186.44. It is known that inhalation of drugs using a spacing device enhances systemic delivery of the medication, this study demonstrates that the delivery of formoterol fumarate from the BAI has exceeded that delivered from the pMDI with spacing device.

Overall the pharmacokinetic results confirmed the hypothesis for the pulmonary deposition (KFL 1501 study) that with the BAI at least 80% of the exposure of the FDC fluticasone propionate/formoterol fumarate observed with the pMDI without spacing device has been achieved. This finding is supportive of efficacy of the fluticasone propionate/formoterol fumarate FDC adminsistered via the BAI. This supports bridging of the efficacy of this fluticasone propionate/formoterol fumarate FDC administered via the BAI to that for the same FDC administered via the pMDI without spacing device.

The formoterol fumarate exposure (as assessed from upper limit of 90% CI) from the BAI compared with that from the pMDI both without and with spacing device were greater than 125%. A pharmacodynamic safety study is needed to establish the safety profile of formoterol fumarate administered via the BAI to ensure that administration of both actives via the BAI is no less safe in respect of systemic absorption than formoterol fumarate administered via the pMDI (without a spacing device – the *a priori* hypothesis) as might be suggested by the pharmacokinetic data presented above.

IV.3 Pharmacodynamics

The Applicant's intention of the pharmacodynamic assessment was to ensure that the ICS-LABA (fluticasone propionate/formoterol fumarate FDC) delivered via a BAI does not pose any safety concerns as compared to same strengths of ICS-LABA delivered via a pMDI (without a spacing device). This study was dependent on the results of the systemic exposure of fluticasone propionate and formoterol fumarate from the systemic pharmacokinetic study as on the basis of these results a decision was taken on whether to assess the pharmacodynamics effect of either the fluticasone propionate or the formoterol fumarate component of these FDC products administered via the BAI and the pMDI without and with spacing device or to assess the pharmacodynamics of both actives. The safety of the fluticasone propionate component of the BAI was not required in view of the fact that the exposure was not greater than that of the pMDI with spacing device from the systemic pharmacokinetic data.

The Applicant assessed the safety profile of formoterol fumarate component of the FDC administered from the BAI and compared with the reference product.

This study followed an adaptive design algorithm which was pre-specified. The pharmacokinetic outcomes from KFL 1503 resulted in the applicant extending the study to assess the long-acting β agonist (formoterol fumarate) mediated pharmacodynamic effects following administration of formoterol fumarate via the BAI compared with administration from the pMDI. A formoterol fumarate inhaler (Atimos Modulite – a pMDI) was used as a comparator.

The pharmacodynamic assessment for formoterol fumarate was performed using a single supratherapeutic dose (1500/60micrograms, i.e. 12 actuations of fluticasone propionate 125µg/formoterol fumarate 5µg) administered via the BAI, the pMDI without spacing device and the pMDI with spacing device; a lower dose (500/20micrograms i.e. 4 actuations of fluticasone propionate 125µg/formoterol fumarate 5µg) administered via the pMDI was included to allow an assessment of assay sensitivity. The formoterol fumarate doses selected for evaluation (60 and 20micrograms) were expected to fall on the steep part of the dose response curve for effects on serum potassium levels. Further decreases in serum potassium would be expected at higher doses, i.e., a plateau in effect was not expected at a dose of 60micrograms.

***Equivalence margins*:**

In the absence of any standardised equivalence margins for relative (safety phamacodynamics) potency, equivalence was defined as the 95% confidence intervals for the ratio of geometric means lying within bounds of 0.5 to 2. The width of the CI (0.5 – 2.0) was based on the known variance between different batches of the same orally inhaled product (OIP). The specifications approved for all OIPs allow a batch to batch fine particle dose variance of up to approximately +/- 45%. This implies that there may be up to a threefold difference in pulmonary dose between different batches of the same OIP. A similar magnitude of variance is allowed for the large particle dose (LPD), which relates to the orally bioavailable fraction. For a PD parameter which exhibits a linear dose response relationship and for an active substance that is orally bioavailable, these variances imply that approximately half as much or twice as much PD effect may be seen with different batches of the same OIP. Hence this CI was considered to be clinically meaningful.

Equivalent safety was assessed by comparing administration of the test product administered via the BAI with the reference product administered via the pMDI without a spacing device (1500/60) or

administered via the pMDI with a spacing device, dependent on whichever of the latter comparators exhibited the greatest systemic effect.

Study Objectives:
The key test of equivalence compared administration of formoterol fumarate in a FDC via the BAI (1500/60 micrograms) with administration via the pMDI without spacing device (1500/60 micrograms) or via the pMDI plus spacing device (1500/60micrograms). A low dose of Flutiform pMDI without spacing device (500/20 micrograms) was included in the study to allow an assessment of assay sensitivity. Atimos pMDI, an approved LABA monotherapy, was included to facilitate further interpretation of the study data.

LABA-mediated effects were assessed by monitoring the primary endpoint – maximum reduction in serum potassium within 4 hours post-dosing.

Other LABA-mediated effects were assessed as secondary endpoints and analysed similar to the primary pharmacodynamics effect:
• Maximum increase in serum glucose from pre-dose to within 4 hours post-dose
• Maximum increase in heart rate from pre-dose to within 4 hours post-dose
• Maximum increase in systolic blood pressure from pre-dose to within 4 hours post-dose
• Maximum reduction in diastolic blood pressure from pre-dose to within 4 hours post-dose

There were also other LABA-mediated effects assessed as secondary endpoints:
• Serum potassium AUC_{0-2} hours post-dose
• Serum glucose AUC_{0-2} hours post-dose
• Heart rate AUC_{0-60} min post-dose
• Systolic blood pressure AUC_{0-60} min post-dose
• Diastolic blood pressure AUC_{0-60} min post-dose.

Serial assessments of serum potassium and glucose, heart rate, diastolic and systolic blood pressure were performed over 6 hours post-dosing. The comparison of treatment-related effects was undertaken within the first 4 hours of this 6-hour period. At 4 hours subjects were given food and thereafter until 6 hours the food effects were analysed across all the parameters measured (serum potassium, serum glucose, heart rate, systolic and diastolic blood pressure) relative to treatment-related effects. The Applicant was interested to contextualise the effect of food on treatment differences.

The pharmacodynamic assessment was conducted after completion of the pharmacokinetic study, it was Part 2 of the study protocol for Study KLF 1503. Although this study is included as part of study protocol for Study KFL 1503, it was carried out as a separate study. None of the participants enrolled into Part 2, the pharmacodynamic study had participated in Part 1, the systemic pharmacokinetic study. The study was conducted following an overnight fasting and subsequently after administering food at 4 hours post-dosing to determine any effects of food on the primary endpoint (serum potassium measurements). All subjects were allocated to receive the following 5 treatments in one of 5 randomised sequences:

Total dose	**Number of puffs**
BAI 1500/60 micrograms	12 puffs of BAI 125/5micrograms
pMDI 1500/60 micrograms without spacing device	12 puffs of pMDI 125/5micrograms
pMDI 1500/60 micrograms with AeroChamber Plus spacing device	12 puffs of pMDI 125/5microgramsmicrograms
pMDI 500/20	4 puffs of 125/5micrograms
pMDI 60 micrograms	5 puffs of 12micrograms

Each treatment phase was separated by a 7-day washout period.

Pharmacodynamic equivalence between treatment comparisons was concluded if the two-sided 95% CI of the treatment ratio (test/reference of the exponentiated least square means) was located completely within the range from 0.5 to 2.0. The Per Protocol (PP) Population was considered as the primary analysis population and only data from subjects that received both of the treatments in the specific comparison were included in the respective statistical analysis model; separate statistical models were run for each comparison of interest. In general, continuous data were summarised by treatment group using the following descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Categorical data were summarised by treatment group as the number and percentage of subjects in each category.

The pharmacodynamic population was defined as all subjects who received at least one dose of the investigational medicinal product (IMP) and had at least one primary pharmacodynamic parameter assessed and all of the pharmacodynamic population without major protocol violations were considered as the PP population for assessment of pharmacodynamic effects.

Primary variable
Table: Statistical Analysis of the Maximum Reduction in Serum Potassium from Pre-Dose Within 4 Hours Post-Dose - PPP

Treatment Group (N)	Exp(LS Mean)	Exp(LS Mean) 95% CI	Ratio (Test/Reference)	95% Confidence Interval
Fluticasone/Formoterol BAI (12 puffs) (33)	0.532	(0.415, 0.682)	0.97	(0.73, 1.28)
Flutiform pMDI With Spacer (12 puffs) (14)*	0.549	(0.455, 0.661)		
Fluticasone/Formoterol BAI (12 puffs) (33)	0.447	(0.262, 0.762)	0.79	(0.43, 1.46)
Flutiform pMDI Without Spacer (12 puffs) (15)*	0.566	(0.369, 0.867)		
Flutiform pMDI Without Spacer (4 puffs) (16)	0.254	(0.169, 0.382)	0.30	(0.17, 0.53)
Flutiform pMDI Without Spacer (12 puffs) (15)*	0.839	(0.614, 1.148)		
Fluticasone/Formoterol BAI (12 puffs) (33)	0.536	(0.458, 0.627)	0.91	(0.73, 1.14)
Atimos Without Spacer (5 puffs) (32)*	0.589	(0.502, 0.690)		
Flutiform pMDI Without Spacer (12 puffs) (15)	0.758	(0.639, 0.899)	1.60	(1.21, 2.12)
Atimos Without Spacer (5 puffs) (32)*	0.473	(0.381, 0.586)		

Cross-reference: Listing 16.2.5.2.1 Group 2) and Table 14.5.1.3 (Group 2).
N: Number of subjects in population. n: Number of subjects with data available in the Per Protocol Population (for both test and reference treatments).
Log transformed values were analysed using ANCOVA with fixed terms for treatment, sequence, period, subject within sequence and baseline as a continuous covariate. The ratio was calculated by transforming the difference between the natural log LS Means back to the original scale.
* Reference treatment for this comparison.

Food is known to have a prominent effect on serum potassium, patients fed at 4 hours post-dose and assessment of food effects on PD variables (from 4 to 6 hours) was used to contextualize any treatment differences that might have been observed. Food effects resulted in a decline in serum potassium levels seen over time after 4 hours.

The maximum reduction in serum potassium with the high dose (pMDI 12 puffs) was 3 times higher compared with the low dose (pMDI 4 puffs, linearly reflecting a threefold dose difference). This finding confirms assay sensitivity.

Effects of formoterol fumarate on serum potassium following administration via the BAI 12 actuations were equivalent to those seen following administration via the pMDI 12 actuations with the spacing device as per the pre-defined equivalence criteria. Equivalence was not shown in the comparison between the BAI 12 actuations and the pMDI 12 actuations without the spacing device, the lower limit of the 95% CI for the treatment ratio was slightly outside (0.44) the lower predefined equivalence margin (0.5 – 2**).** These findings indicate that the safety of formoterol fumarate would be no worse following the administration of 12 actuations of this FDC via the BAI than following the administration of 12 actuations of this FDC via the pMDI with the spacing device (the AeroChamber Plus device).

Secondary Variables

The secondary pharmacodynamics effects included serum potassium up to 2 hours, changes in serum glucose, heart rate, systolic and diastolic blood pressure from baseline to 4 hours. The serum potassium levels were not estimable.

Blood glucose

Table: Statistical Analysis of the Maximum Increase in Plasma Glucose from Pre-Dose Within 4 Hours Post-Dose – PPP

Treatment Group (N)	Exp(LS Mean)	Exp(LS Mean) 95% CI	Ratio (Test/Reference)	95% Confidence Interval
Fluticasone/Formoterol BAI (12 puffs) (33)	0.786	(0.601, 1.027)	1.50	(1.02, 2.21)
Flutiform pMDI With Spacer (12 puffs) (14)*	0.523	(0.413, 0.663)		
Fluticasone/Formoterol BAI (12 puffs) (33)	0.708	(0.542, 0.926)	0.97	(0.63, 1.49)
Flutiform pMDI Without Spacer (12 puffs) (15)*	0.733	(0.527, 1.019)		
Flutiform pMDI Without Spacer (4 puffs) (16)	NE	NE	NE	NE
Flutiform pMDI Without Spacer (12 puffs) (15)*	NE	NE		
Fluticasone/Formoterol BAI (12 puffs) (33)	0.703	(0.557, 0.887)	1.76	(1.26, 2.46)
Atimos Without Spacer (5 puffs) (32)*	0.400	(0.319, 0.501)		
Flutiform pMDI Without Spacer (12 puffs) (15)	0.754	(0.510, 1.117)	1.58	(0.91, 2.75)
Atimos Without Spacer (5 puffs) (32)*	0.476	(0.322, 0.704)		

Cross-reference: Listing 16.2.5.2.1 (Group 2) and Table 14.5.2.3 (Group 2).
N: Number of subjects in population. n: Number of subjects with data available in the Per Protocol Population (for both test and reference treatments).
Log transformed values were analysed using ANCOVA with fixed terms for treatment, sequence, period, subject within sequence and baseline as a continuous covariate. The ratio was calculated by transforming the difference between the natural log LS Means back to the original scale.
* Reference treatment for this comparison.
NE: Not estimable

The assay sensitivity was confirmed with imputed values in individuals with zero or negative maximum changes. The upper limit of 95% confidence interval for serum glucose was greater than the pre-defined equivalence criteria.

Formoterol fumarate component of FDC administered via the BAI/-the same from FDC via the pMDI with spacing device: Upper limit of CI: 2.21. However equivalence criteria was met on comparison of formoterol fumarate delivered via BAI/-pMDI without spacing device. This implies that formoterol fumarate delivered via BAI is safer than pMDI without spacing device, however could be worse than that delivered from pMDI with spacing device.

Heart rate

Table: Statistical Analysis of the Maximum Increase in Heart Rate from Pre- Dose Within 4 Hours Post-Dose - PPP

Treatment Group (N)	Exp(LS Mean)	Exp(LS Mean) 95% CI	Ratio (Test/Reference)	95% Confidence Interval
Fluticasone/Formoterol BAI (12 puffs) (32)	27.65	(20.00, 38.24)	0.66	(0.43, 1.00)
Flutiform pMDI With Spacer (12 puffs) (14)*	41.90	(31.50, 55.74)		
Fluticasone/Formoterol BAI (12 puffs) (32)	29.33	(21.03, 40.89)	1.02	(0.64, 1.62)
Flutiform pMDI Without Spacer (12 puffs) (15)*	28.80	(20.87, 39.73)		
Flutiform pMDI Without Spacer (4 puffs) (16)	26.01	(19.96, 33.91)	0.85	(0.58, 1.26)
Flutiform pMDI Without Spacer (12 puffs) (15)*	30.44	(23.58, 39.29)		
Fluticasone/Formoterol BAI (12 puffs) (32)	30.20	(25.78, 35.37)	1.24	(0.97, 1.57)
Atimos Without Spacer (5 puffs) (31)*	24.45	(20.76, 28.80)		
Flutiform pMDI Without Spacer (12 puffs) (15)	27.55	(22.24, 34.11)	1.27	(0.93, 1.72)
Atimos Without Spacer (5 puffs) (31)*	21.77	(17.45, 27.17)		

Cross-reference: Listing 16.2.5.2.1 and Table 14.5.3.2.
N: Number of subjects in population. n: Number of subjects with data available in the Per Protocol Population (for both test and reference treatments).
Log transformed values were analysed using ANCOVA with fixed terms for treatment, sequence, period, subject within sequence and baseline as a continuous covariate. The ratio was calculated by transforming the difference between the natural log LS Means back to the original scale.
* Reference treatment for this comparison.
Subjects identified as having major deviations with respect specifically to pre-dose heart rate measurements have been removed from this per protocol analysis.

The assay sensitivity was confirmed from the comparison of the test (12 puffs) with the lower dose of formoterol (4 puffs); the increase in heart rate was larger for formoterol fumarate (in the FDC) administered in a dose of 12 puffs from the BAI than when administered in a dose of 4 puffs from a pMDI containing formoterol fumarate alone.

Effects on heart rate from formoterol fumarate delivered via BAI are equivalent to that delivered via pMDI without and with spacing device. Implying that there are no safety concerns with formoterol fumarate delivered via BAI, however these findings are from healthy volunteers and this cannot be extrapolated to patients with compromised cardiovascular conditions.

Systolic Blood Pressure

Table: Statistical Analysis of the Maximum Increase in Systolic Blood Pressure from Pre-Dose Within 4 Hours Post-Dose – PPP

Treatment Group (N)	Exp(LS Mean)	Exp(LS Mean) 95% CI	Ratio (Test/Reference)	95% Confidence Interval
Fluticasone/Formoterol BAI (12 puffs) (33)	17.66	(8.645, 36.08)	1.20	(0.44, 3.29)
Flutiform pMDI With Spacer (12 puffs) (14)*	14.73	(7.216, 30.08)		
Fluticasone/Formoterol BAI (12 puffs) (33)	18.38	(11.86, 28.48)	1.36	(0.73, 2.54)
Flutiform pMDI Without Spacer (12 puffs) (15)*	13.51	(8.722, 20.92)		
Flutiform pMDI Without Spacer (4 puffs) (16)	15.15	(10.50, 21.86)	1.08	(0.64, 1.83)
Flutiform pMDI Without Spacer (12 puffs) (15)*	13.97	(9.669, 20.19)		
Fluticasone/Formoterol BAI (12 puffs) (33)	13.51	(10.60, 17.21)	1.00	(0.70, 1.42)
Atimos Without Spacer (5 puffs) (31)*	13.56	(10.61, 17.35)		
Flutiform pMDI Without Spacer (12 puffs) (15)	10.63	(6.069, 18.63)	0.83	(0.39, 1.78)
Atimos Without Spacer (5 puffs) (31)*	12.77	(7.598, 21.45)		

Cross-reference: Listing 16.2.5.2.1 (Group 2) and Table 14.5.4.2 (Group 2).
N: Number of subjects in population. n: Number of subjects with data available in the Per Protocol Population (for both test and reference treatments).
Log transformed values were analysed using ANCOVA with fixed terms for treatment, sequence, period, subject within sequence and baseline as a continuous covariate. The ratio was calculated by transforming the difference between the natural log LS Means back to the original scale.
* Reference treatment for this comparison.
Subjects identified as having major deviations with respect specifically to pre-dose blood pressure measurements have been removed from this per protocol analysis.

There was a lack of assay sensitivity. Hence comparisons of findings for systolic blood pressure is to be interpreted cautiously.

Effects of formoterol fumarate on any increase in systolic blood pressure following administration via the BAI 12 actuations were greater than those seen following administration via the Flutiform pMDI 12 actuations without and with the spacing device as per the pre-defined equivalence criteria. However due to lack of assay sensitivity, the findings, although suggesting a possible worse systemic safety should be viewed with caution.

Diastolic Blood Pressure

Table: Statistical Analysis of the Maximum Reduction in Diastolic Blood Pressure from Pre-Dose Within 4 Hours Post-Dose – PPP

Treatment Group (N)	Exp(LS Mean)	Exp(LS Mean) 95% CI	Ratio (Test/Reference)	95% Confidence Interval
Fluticasone/Formoterol BAI (12 puffs) (33)	5.902	(3.328, 10.46)	1.13	(0.39, 3.28)
Flutiform pMDI With Spacer (12 puffs) (14)*	5.229	(1.979, 13.82)		
Fluticasone/Formoterol BAI (12 puffs) (33)	NE	NE	NE	NE
Flutiform pMDI Without Spacer (12 puffs) (15)*	NE	NE		
Flutiform pMDI Without Spacer (4 puffs) (16)	3.300	(1.044, 10.44)	0.55	(0.14, 2.06)
Flutiform pMDI Without Spacer (12 puffs) (15)*	6.039	(2.851, 12.79)		
Fluticasone/Formoterol BAI (12 puffs) (33)	7.341	(5.749, 9.373)	1.74	(1.20, 2.53)
Atimos Without Spacer (5 puffs) (31)*	4.216	(3.294, 5.396)		
Flutiform pMDI Without Spacer (12 puffs) (15)	7.450	(3.602, 15.41)	2.01	(0.68, 5.93)
Atimos Without Spacer (5 puffs) (31)*	3.702	(1.743, 7.865)		

Cross-reference: Listing 16.2.5.2.1 (Group 2) and Table 14.5.5.2 (Group 2).
N: Number of subjects in population. n: Number of subjects with data available in the Per Protocol Population (for both test and reference treatments).
Log transformed values were analysed using ANCOVA with fixed terms for treatment, sequence, period, subject within sequence and baseline as a continuous covariate. The ratio was calculated by transforming the difference between the natural log LS Means back to the original scale.
* Reference treatment for this comparison.
Subjects identified as having major deviations with respect specifically to pre-dose blood pressure measurements have been removed from this per protocol analysis
NE: Not estimable

Assay sensitivity was confirmed by the demonstration of an approximate 50% reduction in diastolic pressure following formoterol fumarate pMDI 4 puffs compared with that seen with the FDC administered from pMDI 12, although the difference between treatments was not significant with relatively wide CI around the ratio. The precision of other treatment effect ratios was also low, given relatively low subject numbers and relatively high variability for this parameter, which limits definitive conclusions. Nonetheless the point estimate of the effect ratio for comparison between formoterol fumarate component of FDC delivered as 12 puff from the BAI and pMDI with spacing device was close to 1, potentially suggesting similar effects with these treatments.

Pharmacodynamic conclusion

The pharmcodynamic effects of the formoterol fumarate component of the FDC of fluticasone propionate and formoterol fumarate administered via the BAI were assessed following inhalation of a high dose (12 puffs from the BAI) compared with effects following administration of 12 puffs of the same FDC administered from the pMDI without and with a spacing device and with effects seen with formoterol fumarate alone administered via the pMDI without spacing device.

Thirty five healthy male and female subjects were randomised (7 per sequence). This sample provided at least 90% power to test for pharmacodynamic equivalence defined as a 95% confidence interval for the ratio of geometric means within 0.5 to 2 for each treatment group comparison, with one-sided alpha of 2.5%, assuming 10 dropouts/exclusions from the Per Protocol (PP) Population.

The serum potassium levels, the primary variable in this study indicate that the safety of formoterol fumarate would be no worse following the administration of 12 puffs of this FDC via the BAI than following the administration of 12 puffs of this FDC via the pMDI with the spacing device. Similar findings were seen in plasma glucose, a secondary variable.
Effects on heart rate from formoterol fumarate delivered via BAI are equivalent to that delivered via pMDI without and with spacing device.

Due to lack of assay sensitivity, the findings in respect of systolic and diastolic blood pressure, although suggesting a possible worse systemic safety, are inconclusive and should be viewed with caution.

The key test for equivalence was the comparison of formoterol fumarate administration via the BAI with administration via the pMDI without spacing device (1500/60 microgram) or administration via the pMDI with spacing device, dependent on whichever of the latter comparators exhibited the greatest systemic effect. The results from the pharmacodynamic study demonstrate that based on the primary endpoint (decrease in serum potassium) and secondary endpoint (increase in plasma glucose), the systemic safety of formoterol fumarate administered via the BAI would be no worse than when administered via the pMDI with spacing device.

Although concerns have been raised regarding the justification for the pre-defined equivalence criteria and analysis method, attempting to define new equivalence margins post hoc seems of questionable value; therefore it is considered that the approach should be to assess the potential safety implications of the data for each pharmacodynamic parameter. Using an analysis of difference between BAI and pMDI ± spacer for each parameter, measurements of serum potassium decrease, serum glucose increase and heart rate increase were all numerically in favour of the BAI over the pMDI as regards safety with the exception of serum glucose compared to pMDI + spacer; however, even in this case, at the upper end of the confidence interval there is only a 0.5 mmol/l worsening of glucose increase with BAI compared to the reference.

Furthermore, the pharmacodynamic effects observed in healthy volunteers was from exposure to high doses of formoterol fumarate. i.e 12 puffs = a 60 microgram single dose, whereas the daily recommended dose of the formoterol fumarate component of this FDC (2 puffs twice daily) administered via the BAI, is a maximum daily dose of 40 micrograms. It is unlikely that the above pharmacodynamics effects noticed in healthy volunteers would be seen in patients on recommended doses as low as 20 micrograms (two puffs each administration, taken twice daily).

Overall, these pharmacodynamic data confirm that the systemic safety of formoterol fumarate administered via the BAI is similar to that of formoterol fumarate administered via the pMDI with the spacing device (the AeroChamber Plus device).

Additional data: Patient device handling study (KFL 9501)
The potential advantages of a BAI as per the Applicant is two design features: firstly device resistance is very low, unlike DPIs which are designed with a higher device resistance designed to encourage the patient to inhale hard thereby deagglomerating the powder formulation and generating an aerosol; secondly a BAI requires no manual depression of the canister at the time of inhalation, unlike a pMDI, and thereby removes the need for coordination of these two manoeuvres (inhalation and canister depression). Thus the Applicant claims that BAIs have potential advantages over DPIs and pMDIs which may facilitate successful use in a greater proportion of patients.

The primary objective of the study was to assess whether subjects could successfully use the BAI and pMDI.

Secondary objectives were:
· To assess whether subjects could generate inspiratory flow rates sufficient to trigger the BAI to fire;
· To assess whether subjects could perform all 'critical' steps for the BAI and pMDI successfully;
· To assess whether subjects could be trained to use the device successfully within 15 minutes, a duration approximately replicating the time available for training in a UK General Practice setting. Trained assessors were involved in training and assessing the patients during a training period. The trainer had to watch and listen for the emission of a visible and audible aerosol plume during cap closure, which occurred in the event that a subject failed to trigger the BAI during the inhalation manoeuvre.

Study population
Adolescents and adult subjects with persistent asthma or chronic obstructive pulmonary disease (COPD). Eligible subjects were trained and assessed in the correct handling of each device. Amongst this population approximately 20% were aged 12-17 years (adolescents), 30% were aged >65 years (elderly), 50% were aged 18-65 years (adults).

The population selected included the patients with following categories of airway obstruction
· FEV1 ≥80% predicted
· FEV1 ≥60 to <80% predicted.
· FEV1 <60% predicted.

Study specific inclusion criteria included patients with documented history of asthma or COPD for ≥6 months prior to the screening visit, receiving an ICS and a LABA and able to perform spirometry adequately

Study specific exclusion criteria included clinically unstable disease and serious neuromuscular disorder, or orofacial disease preventing the application of an inhaler to the mouth.

Study end points
The primary endpoint was the percentage of subjects with successful device use, defined as all Steps 1-8 being correctly performed.

The secondary efficacy endpoints were
· The percentage of subjects able to generate an adequate inspiratory flow to trigger the Flutiform BAI;
· The percentage of subjects with successful device use, defined as all critical steps being correctly performed (Steps 2 and 4-6 for the Flutiform pMDI; Steps 2 and 4-7 for the Flutiform BAI);
· The percentage of subjects unable to be trained to use the device successfully within 15 minutes;
· The percentage of subjects able to perform Steps 7, 6, 5, 4, 3, 2 and 1 successfully.

Criteria for assessment of BAI technique

Step	Description
1	Shakes the inhaler well
2	Opens the hinged cap fully
3	Breathes out for at least 2 seconds
4	Places the mouthpiece in the mouth with inhaler in the upright position, with lips sealed firmly around it
5	Breathes in slowly through the mouth
6	Continues to inhale for at least 3 seconds
7	Removes inhaler and closes cap with the inhaler in the upright position
8	Holds breath for at least 4 seconds, then breathes out

Table: Criteria for Assessment of pMDI Technique

Step	Description
1	Shakes the inhaler well
2	Removes the dust cap
3	Breathes out for at least 2 seconds
4	Places the mouthpiece in the mouth with inhaler in the upright position, with lips sealed firmly around it
5	Starts to take a slow deep breath in through the mouth, and actuates the inhaler once by fully depressing the metal canister with/shortly after commencement
6	Continues to inhale for at least 3 seconds
7	Removes inhaler from mouth and replaces cap
8	Holds breath for at least 4 seconds, then breathes out

Table: Summary of Device Handling Success by Subgroups: Per Protocol Population

Subgroup		Flutiform BAI (N=307) n (%)	Flutiform pMDI (N=307) n (%)
FEV_1 % predicted subgroups			
FEV_1 ≥80% predicted	n	116	116
	Successful	99 (85.3)	99 (85.3)
	95% CI for the proportion	(77.6, 91.2)	(77.6, 91.2)
	Unsuccessful	17 (14.7)	17 (14.7)
	95% CI for the proportion	(8.8, 22.4)	(8.8, 22.4)
FEV_1 ≥60 - <80% predicted	n	104	104
	Successful	82 (78.8)	74 (71.2)
	95% CI for the proportion	(69.7, 86.2)	(61.4, 79.6)
	Unsuccessful	22 (21.2)	30 (28.8)
	95% CI for the proportion	(13.8, 30.3)	(20.4, 38.6)
FEV_1 <60% predicted	n	87	87
	Successful	56 (64.4)	64 (73.6)
	95% CI for the proportion	(53.4, 74.4)	(63.0, 82.4)
	Unsuccessful	31 (35.6)	23 (26.4)
	95% CI for the proportion	(25.6, 46.6)	(17.6, 37.0)
Age subgroups			
12 - 17 years	n	66	66
	Successful	52 (78.8)	56 (84.8)
	95% CI for the proportion	(67.0, 87.9)	(73.9, 92.5)
	Unsuccessful	14 (21.2)	10 (15.2)
	95% CI for the proportion	(12.1, 33.0)	(7.5, 26.1)
18 - 65 years	n	166	166
	Successful	136 (81.9)	128 (77.1)
	95% CI for the proportion	(75.2, 87.5)	(70.0, 83.3)
	Unsuccessful	30 (18.1)	38 (22.9)
	95% CI for the proportion	(12.5, 24.8)	(16.7, 30.0)
>65 years	n	75	75
	Successful	49 (65.3)	53 (70.7)
	95% CI for the proportion	(53.5, 76.0)	(59.0, 80.6)
	Unsuccessful	26 (34.7)	22 (29.3)
	95% CI for the proportion	(24.0, 46.5)	(19.4, 41.0)

Table: Summary of the 'Ease of Use' and 'Preferences' Questionnaires: Current Preventer Symbicort Turbohaler: Per Protocol Population

Questionnaire		Flutiform BAI (N=126) n (%)	Flutiform pMDI (N=126) n (%)
Ease of Use Compared to Current Preventer Inhaler	n	126	126
	Much Harder To Use	1 (0.8)	5 (4.0)
	A Bit Harder To Use	25 (19.8)	22 (17.5)
	About As Easy To Use/Don't Know	22 (17.5)	62 (49.2)
	Bit Easier To Use	29 (23.0)	18 (14.3)
	Much Easier To Use	49 (38.9)	19 (15.1)
Preference Compared to Current Preventer Inhaler	n	126	126
	Current Inhaler	25 (19.8)	37 (29.4)
	Study Inhaler	78 (61.9)	58 (46.0)
	No Preference	21 (16.7)	31 (24.6)
	Don't Know	2 (1.6)	-

Conclusions

The purpose of the patient handling study was to establish if patients with different flow rates were able to trigger the BAI when compared with the pMDI. Patients with asthma and COPD with variation in their percent predicted FEV_1 were enrolled. The patient handling study included comparable age groups across the placebo containing BAI and pMDI treatment groups. There were a larger number of male patients than female patients. Inspiratory flow rates were recorded for all patients and were found to be adequate. Sixty four percent of population was asthma patients as compared to only twenty percent of COPD patients.

Patients with asthma and COPD with variation in their percent predicted FEV_1 were enrolled. The percentage of patients (approximately 77%) who were able to successfully complete all inhaler handling steps with the placebo containing BAI was comparable with the percentage who could use the placebo containing pMDI successfully. Overall, 99% of patients were able to generate adequate inspiratory flow to trigger the BAI. Around half of the patients found it easier to use the placebo containing BAI than the inhaler they were using at study entry. A greater percentage of patients with less than 60% predicted FEV_1 and aged above 65 years had difficulty triggering the BAI as compared with the pMDI.

IV.4 Clinical efficacy & IV.5 Clinical safety

In the pulmonary pharmacokinetic study (KFL 1501) main phase, 7 (14.9%) subjects reported 13 AEs which were considered related to study medication: 7 under fluticasone/formoterol BAI treatment, 4 under Flutiform pMDI with spacer treatment and 2 under Flutiform pMDI without spacer treatment – 11 events of headache, one event each of nausea and laryngeal discomfort. One subject experienced a severe AE of headache. No subjects reported SAEs in this study. One subject was discontinued from the study after experiencing AEs of diarrhoea, nausea and vomiting

In the systemic pharmacokinetic study (KFL1503 stage 1), 22 subjects (45.8%) experienced 33 AEs. None of the AEs were considered to be treatment related or severe in intensity. No SAEs were reported. Two subjects were discontinued from the study – one subject who experienced an AE of flu symptoms with BAI and one subject who experienced an AE of chest infection with pMDI.

In the pharmacodynamic study (KFL1503 stage 2), 23 (65.7%) subjects experienced 44 AEs out of which 17 AEs were considered as possibly related to study treatment. These included tachycardia, headache and dizziness. No SAEs were reported and none of the subjects were discontinued from the study due to an AE. It should be noted that these AEs were reported with supratherapeutic doses., Therefore the clinical interpretation must be made with caution.. However similar adverse events are known to occur at therapeutic doses as mentioned in the product information of authorised Flutiform pMDI.

There were no deaths in any study.

Other safety assessments including vital signs, ECG showed no clinically significant abnormalities. Any shifts noted from normal range in the mean values for haematology, blood chemistry and urinalysis parameters revealed that no shift was of clinical concern for any laboratory parameter.

The pharmacokinetic and pharmacodynamic studies presented have established the safety and efficacy of fluticasone propionate and formoterol fumarate administered via BAI when compared with the same FDC of fluticasone propionate and formoterol fumarate administered via the pMDI

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 Flutiform/Affera/Abriff K-haler.

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

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	Cardiac arrhythmias Cardiac ischaemia Hyperglycaemia Asthma exacerbations Psychological or behavioural effects
Important potential risks	Anaphylactic reactions Adrenal suppression Growth retardation Decrease in bone mineral density QTc interval prolongation Serious asthma- related events Paradoxical bronchospasm Cataract Glaucoma Hypokalaemia Off-label use
Missing information	Subjects with hepatic impairment Subjects with renal impairment Current smoking history Long-term safety and efficacy of the new combination of fluticasone and HFA 227 (propellant)

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

IV.7 Discussion on the clinical aspects

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

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.

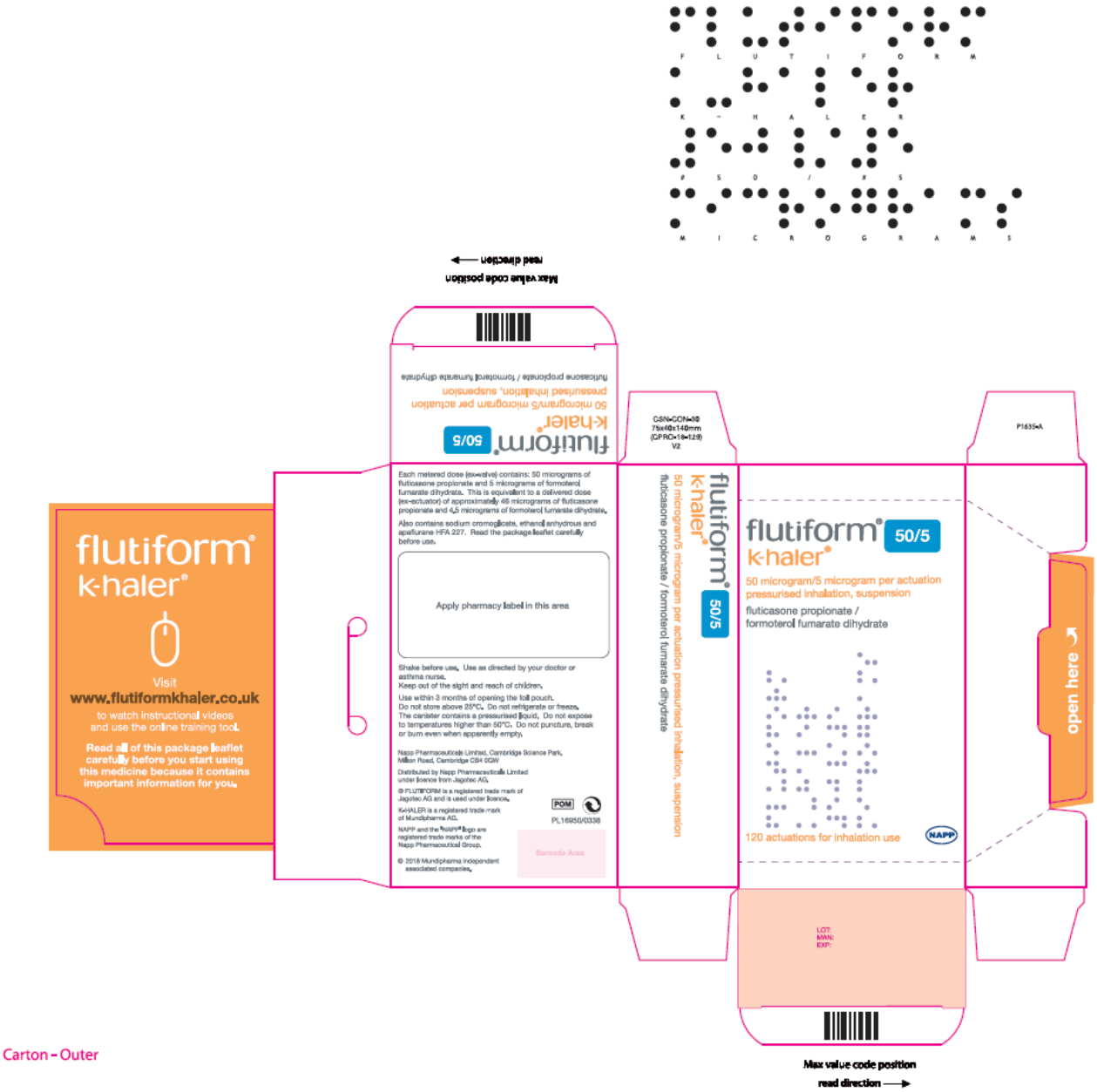
The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI Overall conclusion, benefit/risk assessment and recommendation

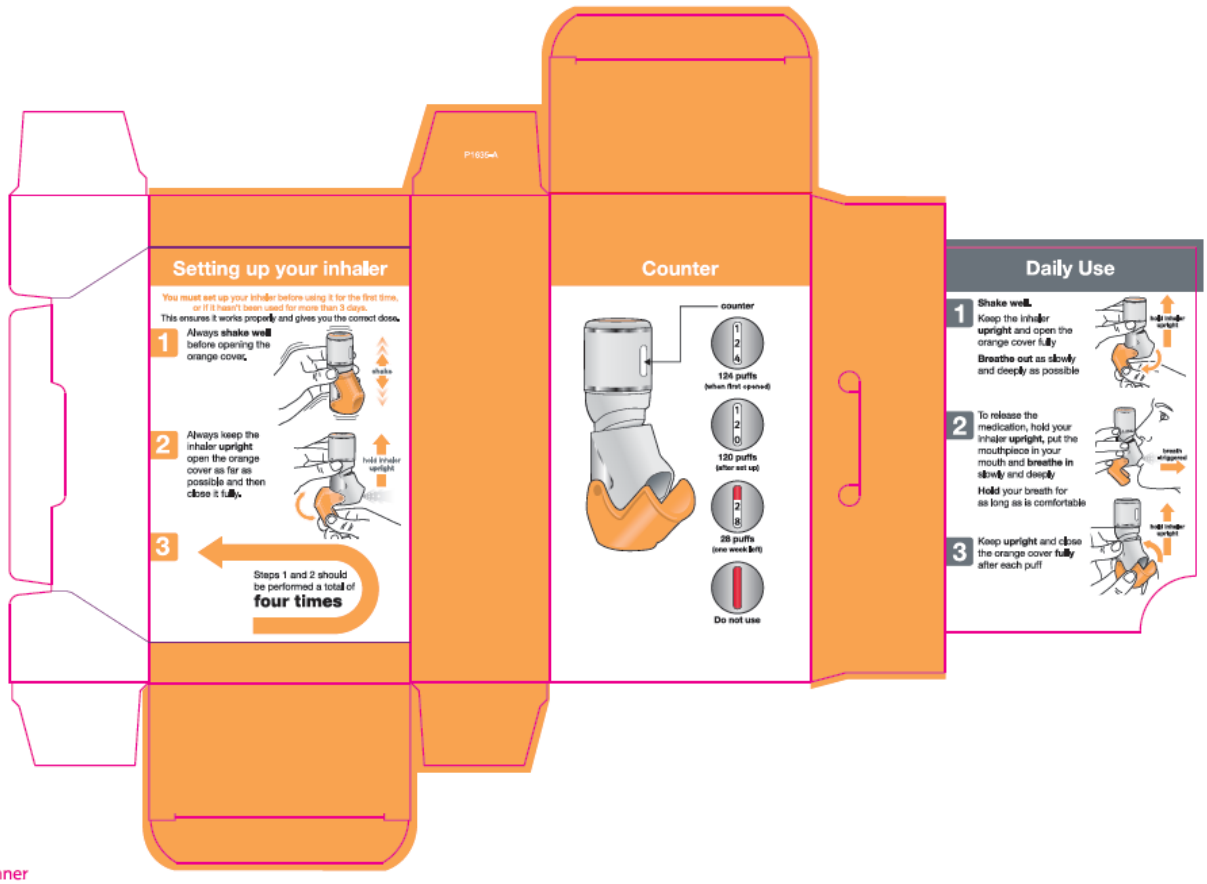
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fluticasone propionate and formoterol fumarate dihydrate is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk 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 (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 Flutiform K-haler is presented below:

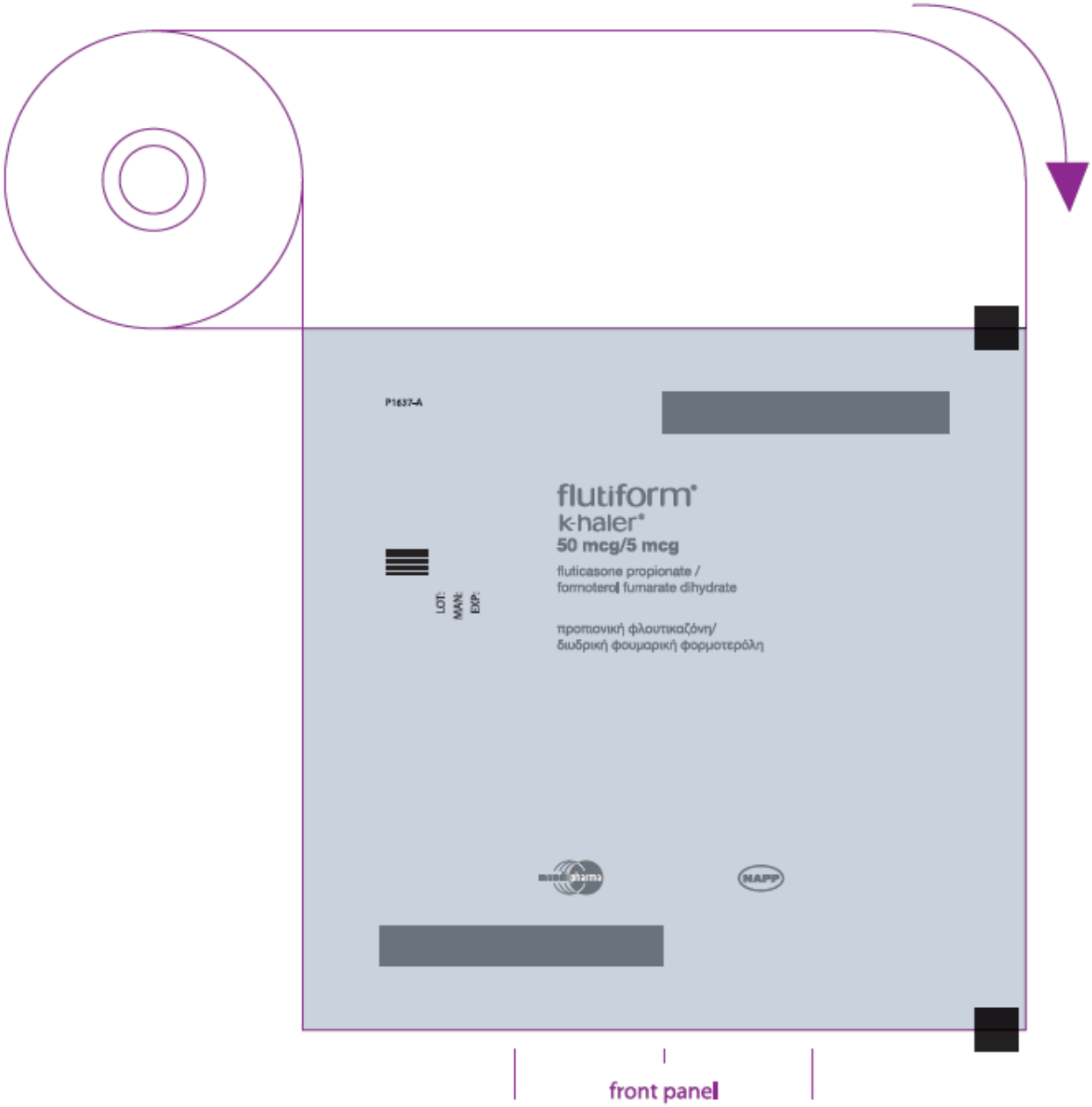


Carton – Outer

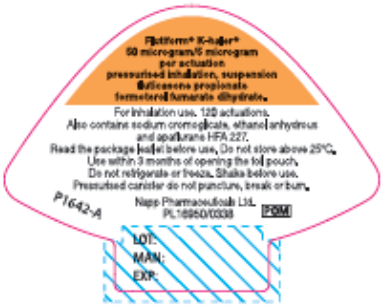


Carton - Inner

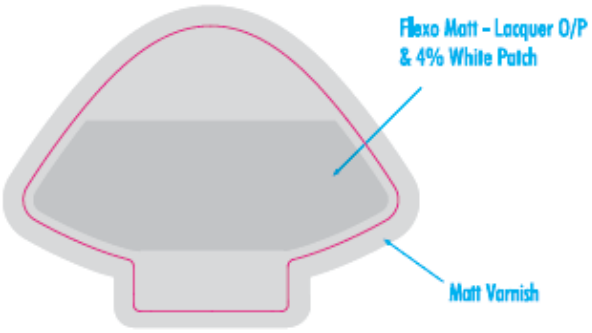
NAPP LABEL DRAWING No: FSN-CON-02
165 x 170 mm (CPRO-24-9)
V4



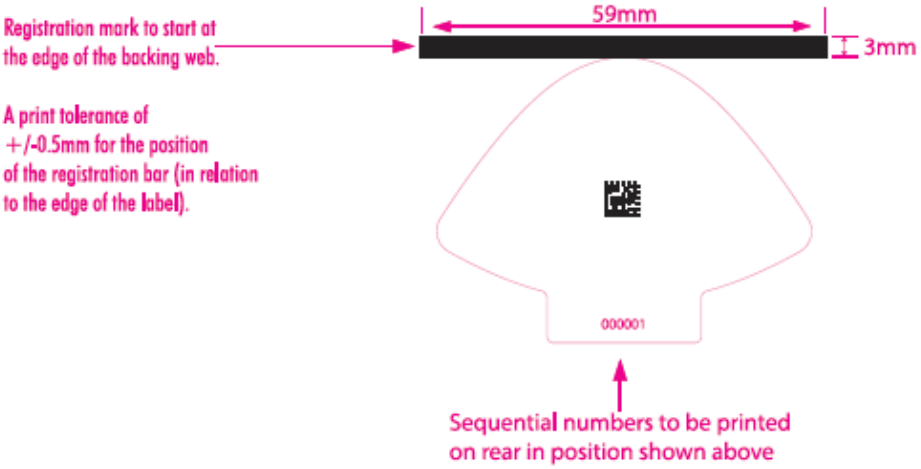
NAPP LABEL DRAWING NO: LBSN-CON-36
54.36 x 41.41 mm (CPRO-14-107)
V2



FRONT - VARNISH AREAS
(FOR PRINTING PURPOSES ONLY)

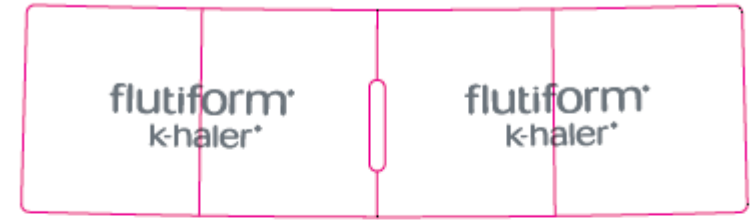


REVERSE BACKING MATERIAL

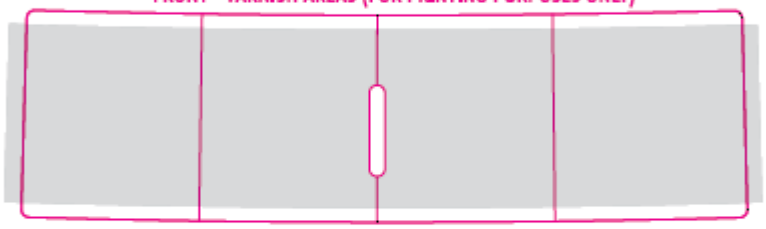


Sequential numbers to be printed
on rear in position shown above

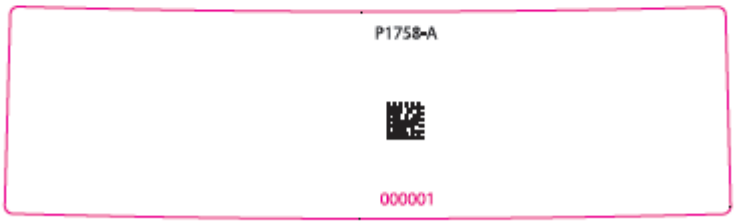
NAPP LABEL DRAWING NO: LSBN-CON-33
99.28 x 28.65 mm (CPRO-14-109)
V2



FRONT - VARNISH AREAS (FOR PRINTING PURPOSES ONLY)



REVERSE BACKING MATERIAL



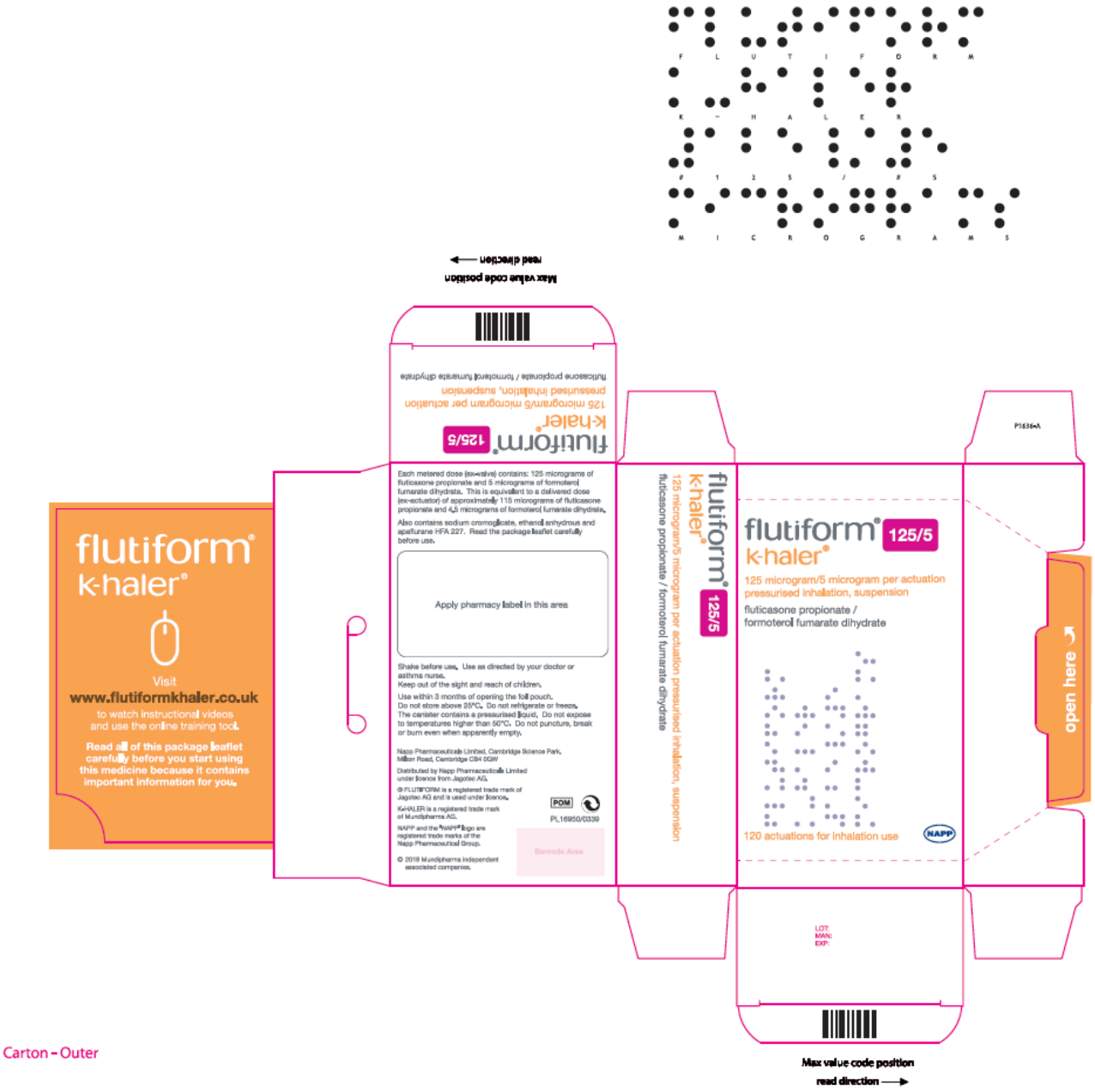
Sequential numbers to be printed
on rear in position shown above

NAPP LABEL DRAWING NO: LSBN-CON-32
16 x 16 mm (CPRO-14-108)
V2

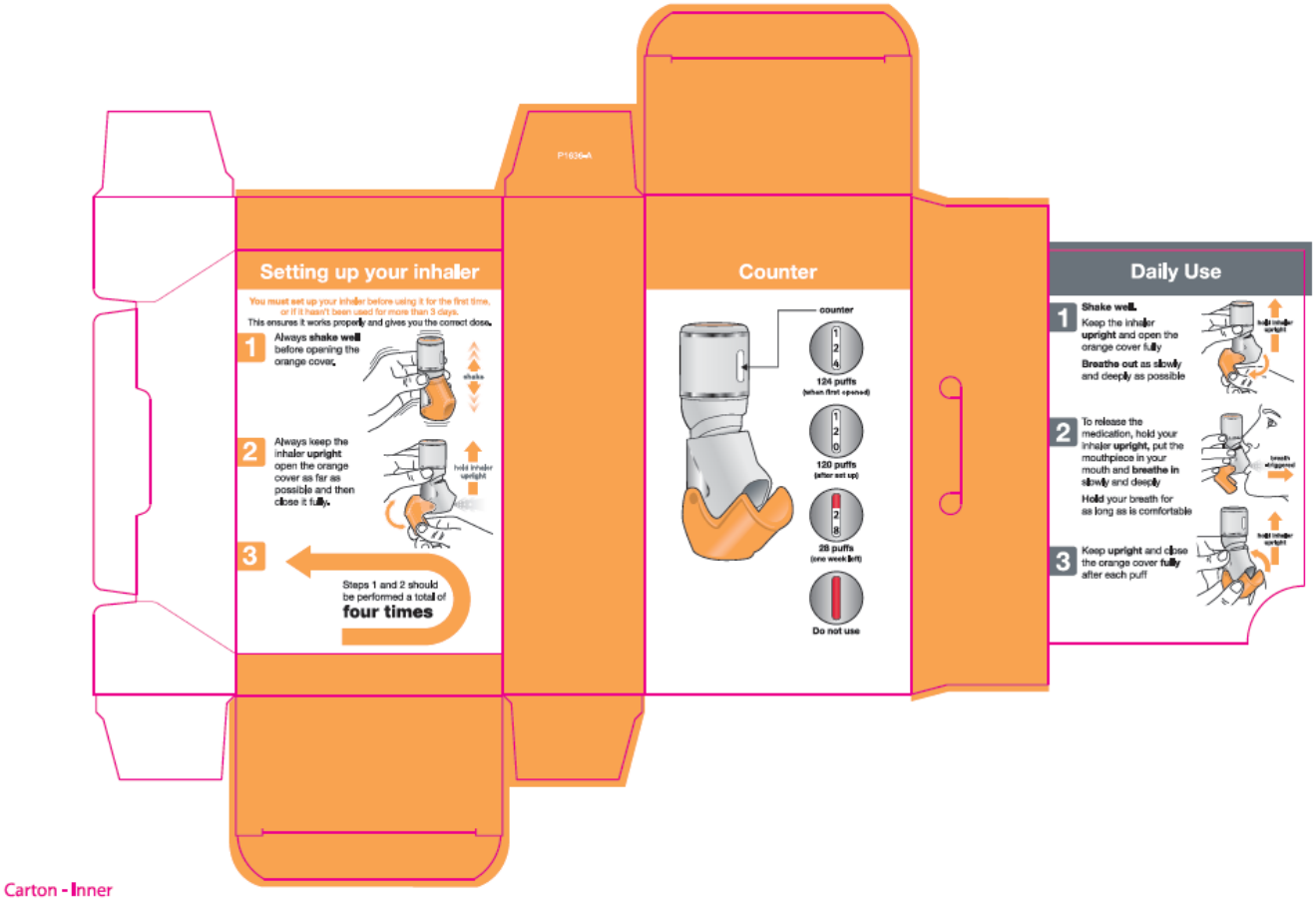
FRONT

BACK

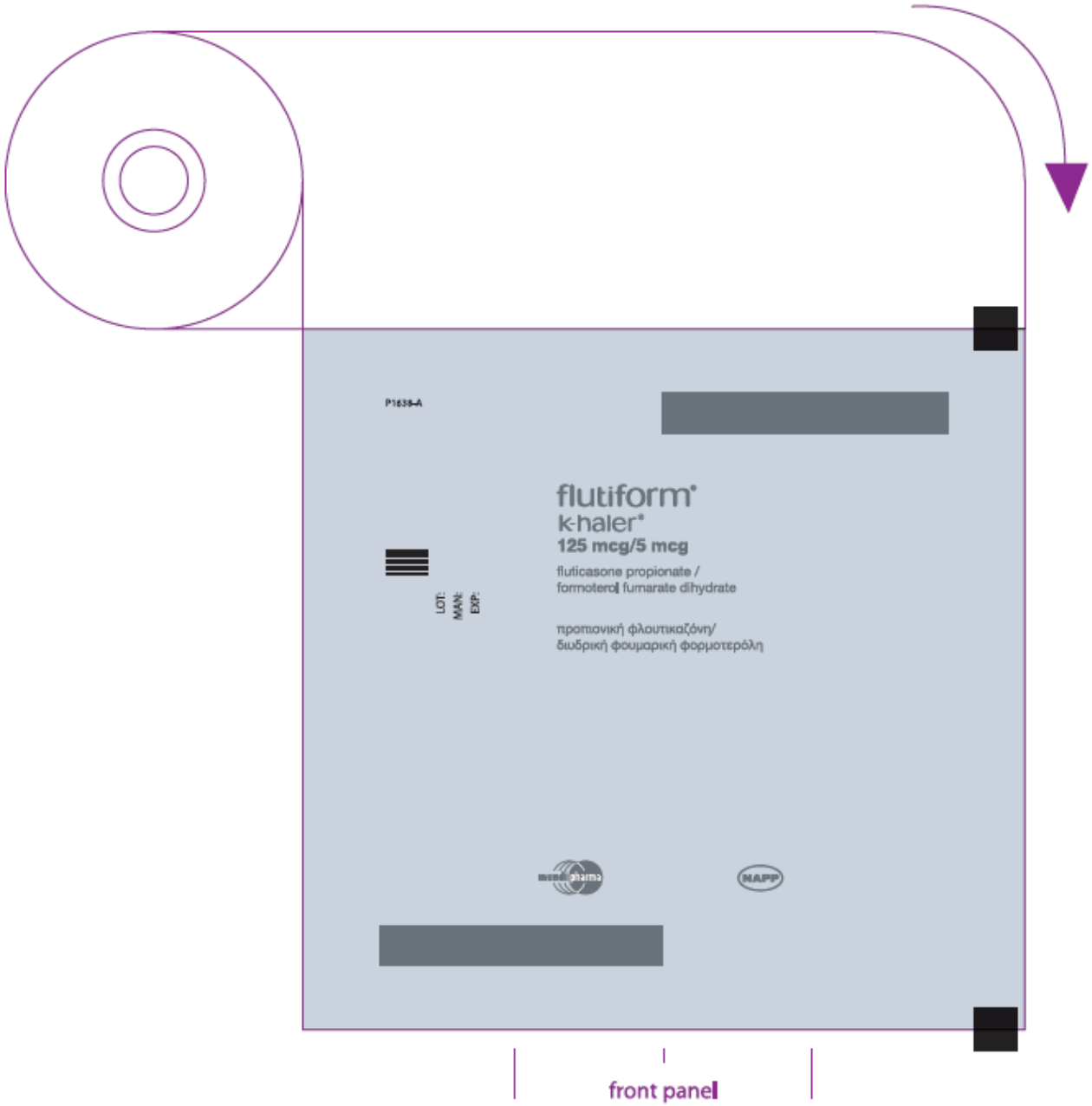
Sequential numbers to be printed
on rear in position shown above

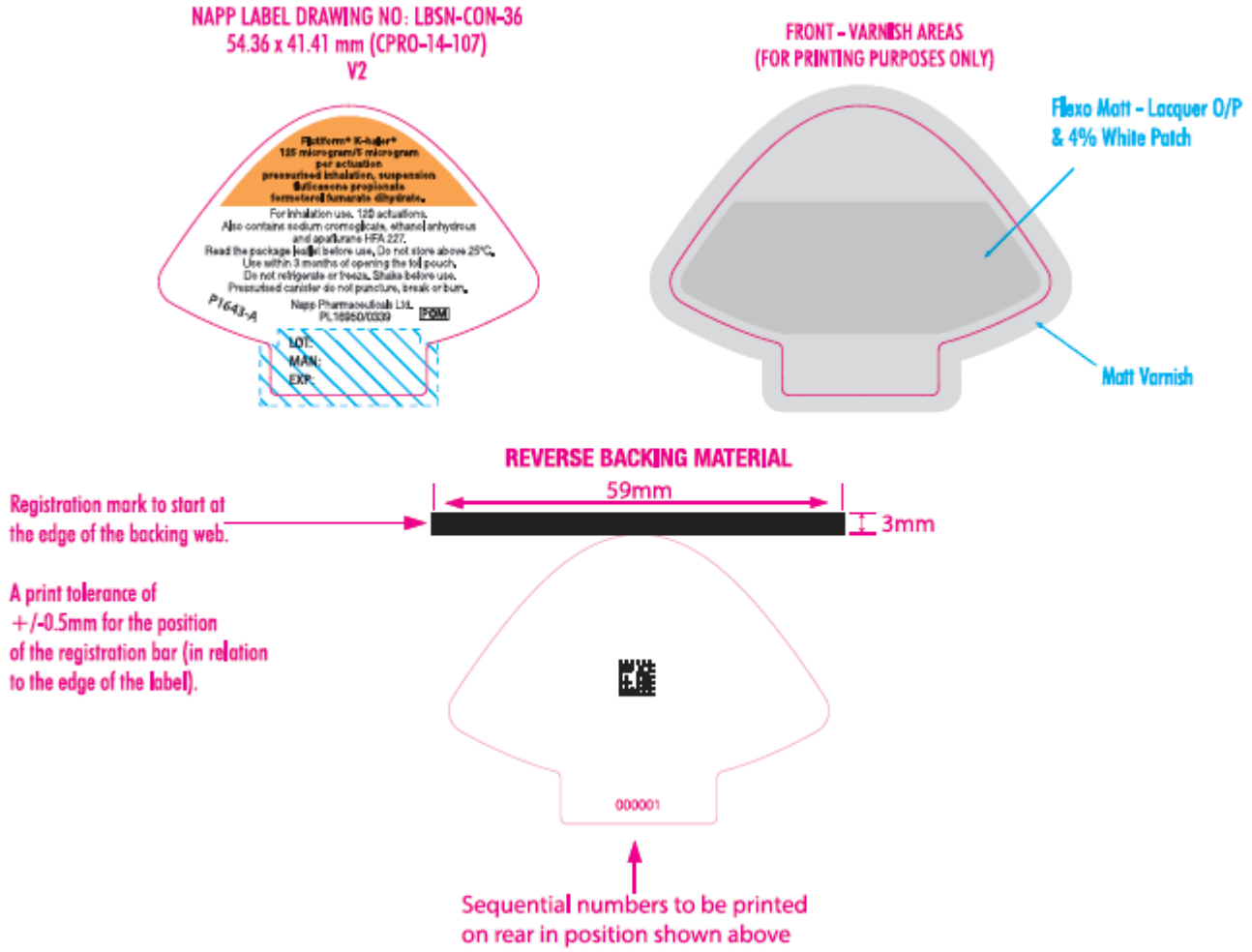


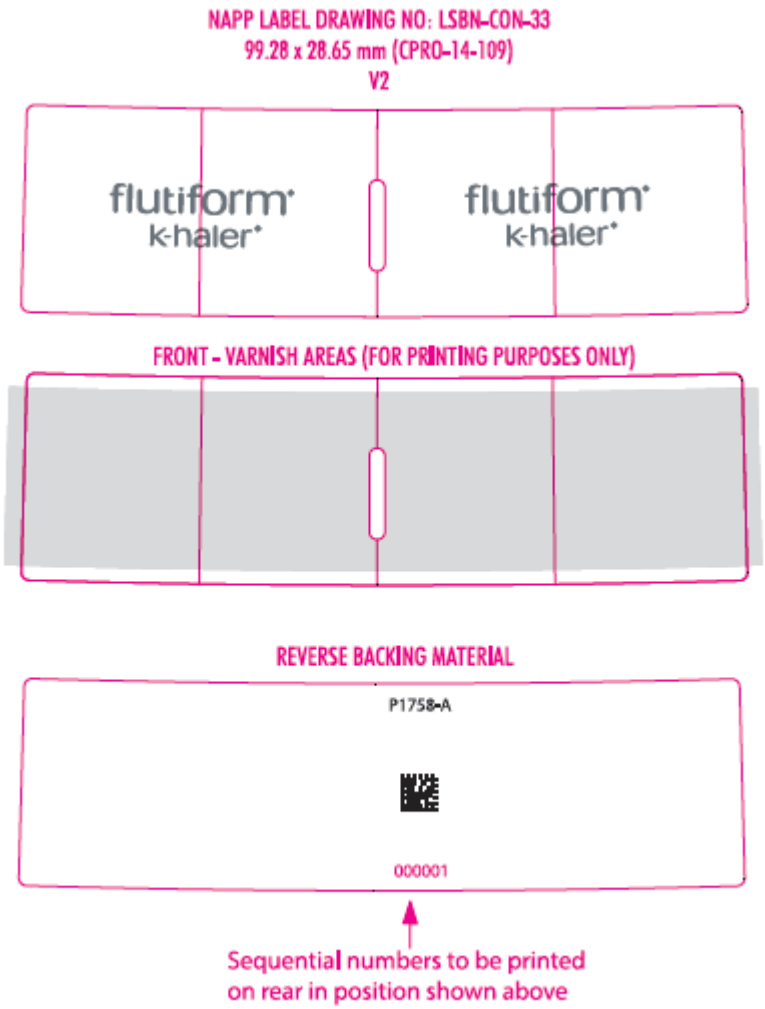
Carton - Outer


Setting up your inhaler
You must set up your inhaler before using it for the first time, or if it hasn't been used for more than 3 days.
This ensures it works properly and gives you the correct dose.
1 Always shake well before opening the orange cover.
shake
2 Always keep the inhaler upright open the orange cover as far as possible and then close it fully.
hold inhaler upright
3
Steps 1 and 2 should be performed a total of four times
Counter
counter
124 puffs
(when first opened)
120 puffs
(after set up)
28 puffs
(one week left)
Do not use
Daily Use
1 Shake well.
Keep the inhaler upright and open the orange cover fully
Breathe out as slowly and deeply as possible
hold inhaler upright
2 To release the medication, hold your inhaler upright, put the mouthpiece in your mouth and breathe in slowly and deeply
Hold your breath for as long as is comfortable
breath stopped
3 Keep upright and close the orange cover fully after each puff
hold inhaler upright
Carton - Inner

NAPP LABEL DRAWING No: FSN-CON-02
165 x 170 mm (CPRO-24-9)
V4




NAPP LABEL DRAWING NO: LBSN-CON-36
54.36 x 41.41 mm (CPRO-14-107)
V2
For inhalation use. 120 actuations.
Also contains sodium cromoglicate, ethanol anhydrous
and apafluorane HFA 227.
Use within 3 months of opening the foil pouch.
Do not refrigerate or freeze. Shake before use.
Napp Pharmaceuticals Ltd.
POM
LOT:
MAN:
EXP:
FRONT - VARNISH AREAS
(FOR PRINTING PURPOSES ONLY)
Flexo Matt - Lacquer O/P
& 4% White Patch
Matt Varnish
REVERSE BACKING MATERIAL
59mm
3mm
Registration mark to start at
the edge of the backing web.
A print tolerance of
+/-0.5mm for the position
of the registration bar (in relation
to the edge of the label).
000001
Sequential numbers to be printed
on rear in position shown above


NAPP LABEL DRAWING NO: LSBN-CON-33
99.28 x 28.65 mm (CPRO-14-109)
V2
flutiform
k-haler
flutiform
k-haler
FRONT - VARNISH AREAS (FOR PRINTING PURPOSES ONLY)
REVERSE BACKING MATERIAL
P1758-A
000001
Sequential numbers to be printed
on rear in position shown above

NAPP LABEL DRAWING NO: LSBN-CON-32
16 x 16 mm (CPRO-14-108)
V2

FRONT

BACK

Sequential numbers to be printed
on rear in position shown above

The following text is the approved label text for Affera/Abriff K-haler, no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

affera® k-haler® 50 microgram/ 5 microgram per actuation

pressurised inhalation, suspension
fluticasone propionate / formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each metered dose (ex-valve) contains:
50 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 46 micrograms of fluticasone propionate and 4.5 micrograms of formoterol fumarate dihydrate.

3. LIST OF EXCIPIENTS

Also contains sodium cromoglicate, ethanol anhydrous and apaflurane HFA 227.Read the package leaflet carefully before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation suspension
120 actuations

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use.
Shake before use. Use as directed by your doctor or asthma nurse.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 months of opening the foil pouch.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not refrigerate or freeze.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

<Not applicable>

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW

12. MARKETING AUTHORISATION NUMBER(S)

PL 16950/0350

13. BATCH NUMBER

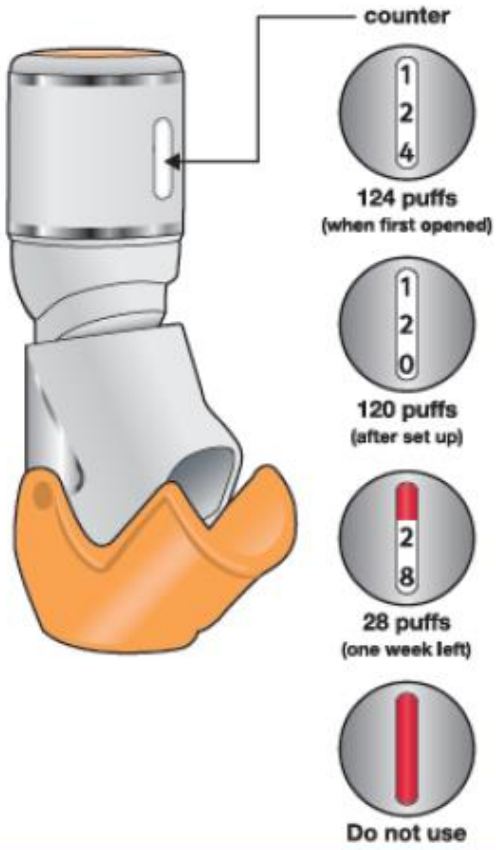
LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM
{See Blue Box for National Requirements}

15. INSTRUCTIONS ON USE

Counter



Setting up your inhaler

You must set up your inhaler before using it for the first time, or if it hasn't been used for more than 3 days.
This ensures it works properly and gives you the correct dose.

1 Always **shake well** before opening the orange cover.

2 Always keep the inhaler **upright** open the orange cover as far as possible and then close it fully.

3 Steps 1 and 2 should be performed a total of **four times**

Visit www.XXXXkhaler.co.ukto watch instructional videos and use the online training tool.

16. INFORMATION IN BRAILLE

affera k-haler 50/5 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

Other :

MAN

Apply pharmacy label in this area.

Distributed by Napp Pharmaceuticals Limited under licence from Jagotec AG.

® AFFERA is a registered trade mark of Jagotec AG and is used under licence.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

FLOW WRAP

1. NAME OF THE MEDICINAL PRODUCT

affera® k-haler® 50 mcg /5 mcg

fluticasone propionate / formoterol fumarate dihydrate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Napp

Mundipharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

MAN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ACTUATOR LABEL – IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

affera® k-haler® 50 microgram/ 5 microgram per actuation

pressurised inhalation, suspension

fluticasone propionate / formoterol fumarate dihydrate

2. METHOD OF ADMINISTRATION

For inhalation use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 actuations

6. OTHER

Also contains sodium cromoglicate,ethanol anhydrous and apaflurane HFA 227.

Read the package leaflet before use.

Do not store above 25ºC.
Use within 3 months of opening the foil pouch.
Do not refrigerate or freeze.
Shake before use.
Pressurised canister do not puncture, break or burn.

Napp Pharmaceuticals Ltd
PL 16950/0350
POM

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

affera® *k-haler*® 125 microgram/5 microgram per actuation

pressurised inhalation, suspension
fluticasone propionate / formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each metered dose (ex-valve) contains:
125 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 115 micrograms of fluticasone propionate and 4.5 micrograms of formoterol fumarate dihydrate.

3. LIST OF EXCIPIENTS

Also contains sodium cromoglicate, ethanol anhydrous and apaflurane HFA 227.Read the package leaflet carefully before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation suspension
120 actuations

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use.
Shake before use. Use as directed by your doctor or asthma nurse.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 months of opening the foil pouch.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.
Do not refrigerate or freeze.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

<Not applicable>

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW

12. MARKETING AUTHORISATION NUMBER(S)

PL 16950/0351

13. BATCH NUMBER

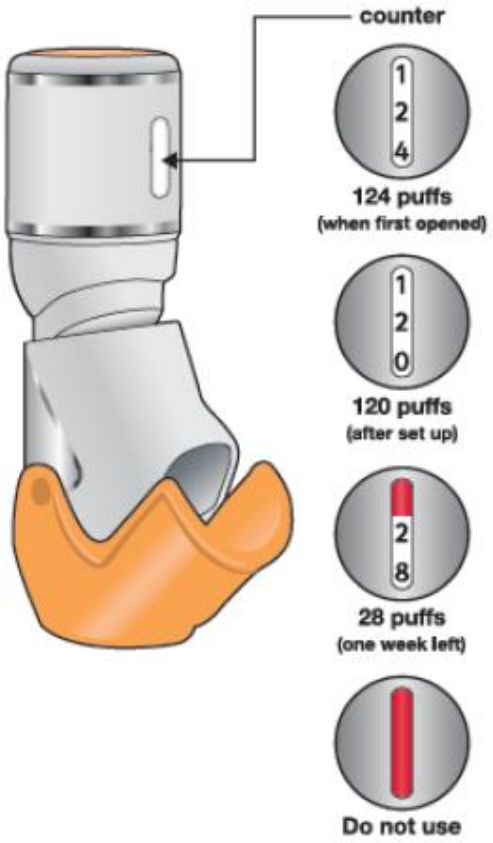
LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM
{See Blue Box for National Requirements}

15. INSTRUCTIONS ON USE

Counter



Setting up your inhaler

You must set up your inhaler before using it for the first time, or if it hasn't been used for more than 3 days.

This ensures it works properly and gives you the correct dose.

1 Always **shake well** before opening the orange cover.

2 Always keep the inhaler **upright** open the orange cover as far as possible and then close it fully.

3

Steps 1 and 2 should be performed a total of **four times**

Visit www.XXXXkhaler.co.ukto watch instructional videos and use the online training tool.

16. INFORMATION IN BRAILLE

affera k-haler 125/5 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

Other :

MAN

Apply pharmacy label in this area.

Distributed by Napp Pharmaceuticals Limited under licence from Jagotec AG.

® AFFERA is a registered trade mark of Jagotec AG and is used under licence.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

FLOW WRAP

1. NAME OF THE MEDICINAL PRODUCT

affera® *k-haler*® 125 mcg /5 mcg

fluticasone propionate / formoterol fumarate dihydrate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Napp

Mundipharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

MAN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ACTUATOR LABEL – IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

affera® k-haler® 125 microgram/ 5 microgram per actuation

pressurised inhalation, suspension

fluticasone propionate / formoterol fumarate dihydrate

2. METHOD OF ADMINISTRATION

For inhalation use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 actuations

6. OTHER

Also contains sodium cromoglicate,ethanol anhydrous and apaflurane HFA 227.

Read the package leaflet before use.

Do not store above 25ºC.
Use within 3 months of opening the foil pouch.
Do not refrigerate or freeze.
Shake before use.
Pressurised canister do not puncture, break or burn.

Napp Pharmaceuticals Ltd
PL 16950/0351
POM

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

abriff® k-haler® 50 microgram/ 5 microgram per actuation

pressurised inhalation, suspension
fluticasone propionate / formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each metered dose (ex-valve) contains:
50 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 46 micrograms of fluticasone propionate and 4.5 micrograms of formoterol fumarate dihydrate.

3. LIST OF EXCIPIENTS

Also contains sodium cromoglicate, ethanol anhydrous and apaflurane HFA 227.Read the package leaflet carefully before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation suspension
120 actuations

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use.
Shake before use. Use as directed by your doctor or asthma nurse.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 months of opening the foil pouch.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not refrigerate or freeze.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

<Not applicable>

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW

12. MARKETING AUTHORISATION NUMBER(S)

PL 16950/0352

13. BATCH NUMBER

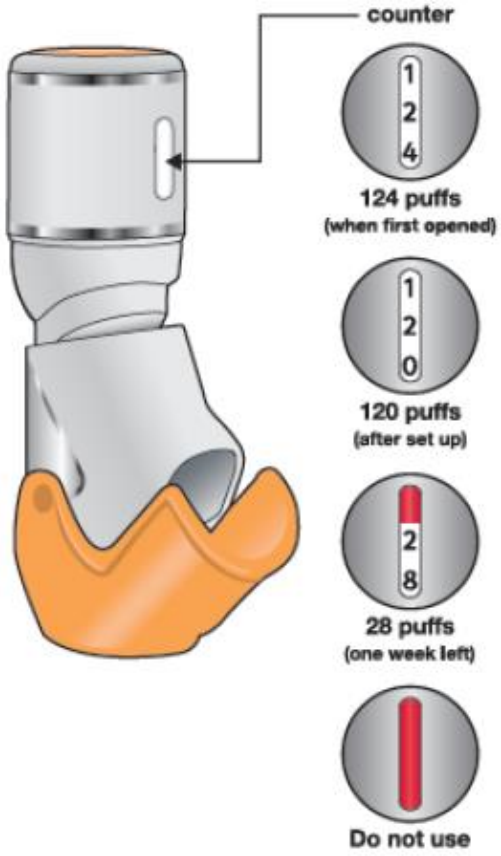
LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM
{See Blue Box for National Requirements}

15. INSTRUCTIONS ON USE

Counter



Setting up your inhaler

You must set up your inhaler before using it for the first time, or if it hasn't been used for more than 3 days.
This ensures it works properly and gives you the correct dose.

1 Always **shake well** before opening the orange cover.

2 Always keep the inhaler **upright** open the orange cover as far as possible and then close it fully.

3

Steps 1 and 2 should be performed a total of **four times**

Visit www.XXXXkhaler.co.uk to watch instructional videos and use the online training tool.

16. INFORMATION IN BRAILLE

abriff k-haler 50/5 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

Other :

MAN

Apply pharmacy label in this area.

Distributed by Napp Pharmaceuticals Limited under licence from Jagotec AG.

® ABRIFF is a registered trade mark of Jagotec AG and is used under licence.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

FLOW WRAP

1. NAME OF THE MEDICINAL PRODUCT

abriff® k-haler® 50 mcg /5 mcg

fluticasone propionate / formoterol fumarate dihydrate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Napp

Mundipharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

MAN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ACTUATOR LABEL – IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

abriff® k-haler® 50 microgram/ 5 microgram per actuation

pressurised inhalation, suspension

fluticasone propionate / formoterol fumarate dihydrate

2. METHOD OF ADMINISTRATION

For inhalation use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 actuations

6. OTHER

Also contains sodium cromoglicate,ethanol anhydrous and apaflurane HFA 227.

Read the package leaflet before use.

Do not store above 25°C.
Use within 3 months of opening the foil pouch.
Do not refrigerate or freeze.
Shake before use.
Pressurised canister do not puncture, break or burn.

Napp Pharmaceuticals Ltd
PL 16950/0352
POM

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

abriff® *k-haler*® 125 microgram/5 microgram per actuation

pressurised inhalation, suspension
fluticasone propionate / formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each metered dose (ex-valve) contains:
125 micrograms of fluticasone propionate and 5 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 115 micrograms of fluticasone propionate and 4.5 micrograms of formoterol fumarate dihydrate.

3. LIST OF EXCIPIENTS

Also contains sodium cromoglicate, ethanol anhydrous and apaflurane HFA 227.Read the package leaflet carefully before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Pressurised inhalation suspension
120 actuations

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use.
Shake before use. Use as directed by your doctor or asthma nurse.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 months of opening the foil pouch.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.
Do not refrigerate or freeze.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

<Not applicable>

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW

12. MARKETING AUTHORISATION NUMBER(S)

PL 16950/0353

13. BATCH NUMBER

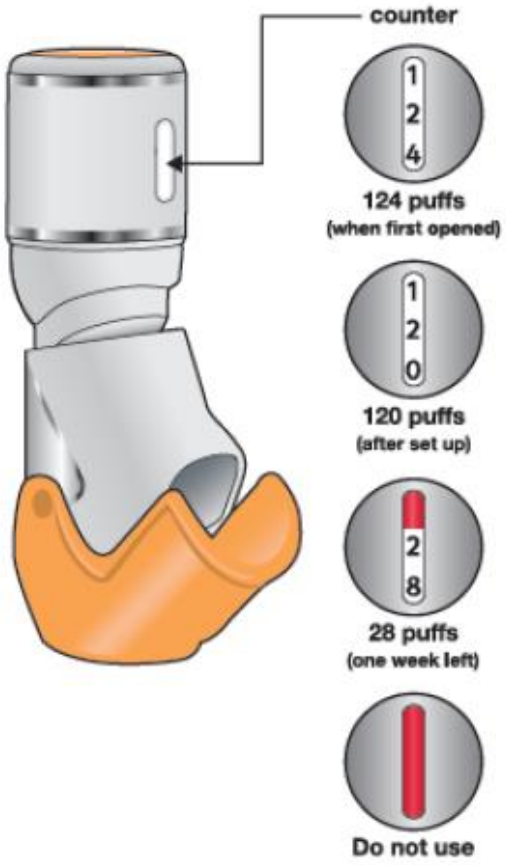
LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM
{See Blue Box for National Requirements}

15. INSTRUCTIONS ON USE

Counter



Setting up your inhaler

You must set up your inhaler before using it for the first time, or if it hasn't been used for more than 3 days.
This ensures it works properly and gives you the correct dose.

1 Always **shake well** before opening the orange cover.

2 Always keep the inhaler **upright** open the orange cover as far as possible and then close it fully.

3 Steps 1 and 2 should be performed a total of **four times**

Visit www.XXXXkhaler.co.ukto watch instructional videos and use the online training tool.

16. INFORMATION IN BRAILLE

abriff k-haler 125/5 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

Other :

MAN

Apply pharmacy label in this area.

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MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

FLOW WRAP

1. NAME OF THE MEDICINAL PRODUCT

abriff® k-haler® 125 mcg /5 mcg

fluticasone propionate / formoterol fumarate dihydrate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Napp

Mundipharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

MAN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ACTUATOR LABEL – IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

abriff® k-haler® 125 microgram/ 5 microgram per actuation

pressurised inhalation, suspension

fluticasone propionate / formoterol fumarate dihydrate

2. METHOD OF ADMINISTRATION

For inhalation use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 actuations

6. OTHER

Also contains sodium cromoglicate,ethanol anhydrous and apaflurane HFA 227.

Read the package leaflet before use.

Do not store above 25ºC.
Use within 3 months of opening the foil pouch.
Do not refrigerate or freeze.
Shake before use.
Pressurised canister do not puncture, break or burn.

Napp Pharmaceuticals Ltd
PL 16950/0353
POM

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
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