Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

AirBuFo Forspiro 160 microgram/4.5 microgram/dose inhalation powder, pre-dispensed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (inhaled dose) contains 160 micrograms of budesonide and 4.5 micrograms of formoterol fumarate dihydrate.

Each metered dose (pre-dispensed dose contained in the blister) contains 194.7 micrograms of budesonide and 6.1 micrograms of formoterol fumarate dihydrate.

Excipient with known effect
Lactose monohydrate: 5.4 mg per metered doseand 4.4 mg per delivered dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.

White to off-white or slightly yellow powder with no agglomerates.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
AirBuFo Forspiro is indicated in adults and adolescents (12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β_2 adrenoceptor agonist) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β_2 adrenoceptor agonists.
or
- patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists.

Chronic Obstructive Pulmonary Disease (COPD)
AirBuFo Forspiro is indicated in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV_1) <70% predicted normal (post bronchodilator) and an exacerbation history despite regular bronchodilator therapy (see also section 4.4).

4.2 Posology and method of administration

Route of administration: for inhalation use.
Posology

Asthma
AirBuFo Forspiro is not intended for the initial management of asthma. The required dose of each component of AirBuFo Forspiro is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the maintenance dose is adjusted. If an individual patient should require a combination of doses other than that available in the combination inhaler, appropriate doses of β_2 adrenoceptor agonists and/or corticosteroids by individual inhalers should be prescribed.

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Patients should be regularly reassessed by their prescriber/health care provider so that the dose of budesonide/formoterol remains optimal. When

long-term control of symptoms is maintained with the lowest recommended dose, then the next step could include a test of inhaled corticosteroid alone.

When it is appropriate to titrate down to a lower strength or to prescribe a higher strength than is available for AirBuFo Forspiro, a change to an alternative fixed-dose combination of budesonide and formoterol fumarate containing a lower or a higher dose of the inhaled corticosteroid, respectively, is required.

For AirBuFo Forspiro there are two treatment approaches:

A. AirBuFo Forspiro maintenance therapy: AirBuFo Forspiro is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue.
B. AirBuFo Forspiro maintenance and reliever therapy: AirBuFo Forspiro is taken as regular maintenance treatment and as needed in response to symptoms.

A. AirBuFo Forspiro maintenance therapy
Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Recommended doses:

Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.

Adolescents (12 – 17 years): 1-2 inhalations twice daily.

In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include AirBuFo Forspiro given once daily, when in the opinion of the prescriber, a long-acting bronchodilator in combination with an inhaled corticosteroid would be required to maintain control.
Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Children under 12 years: As no data are available, AirBuFo Forspiro is not recommended for children younger than 12 years.

B. AirBuFo Forspiro maintenance and reliever therapy
Patients take a daily maintenance dose of AirBuFo Forspiro and in addition take AirBuFo Forspiro as needed in response to symptoms. Patients should be advised to always have AirBuFo Forspiro available for rescue use.

AirBuFo Forspiro maintenance and reliever therapy should especially be considered for patients with:
- inadequate asthma control and in frequent need of reliever therapy
- asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse reactions is needed in patients who frequently take high numbers of AirBuFo Forspiro as-needed inhalations.

Recommended doses:

Adults and adolescents (12 years and older): The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.

Children under 12 years: AirBuFo Forspiro maintenance and reliever therapy is not recommended for children.

COPD
Recommended doses:

Adults: 2 inhalations twice daily

General information

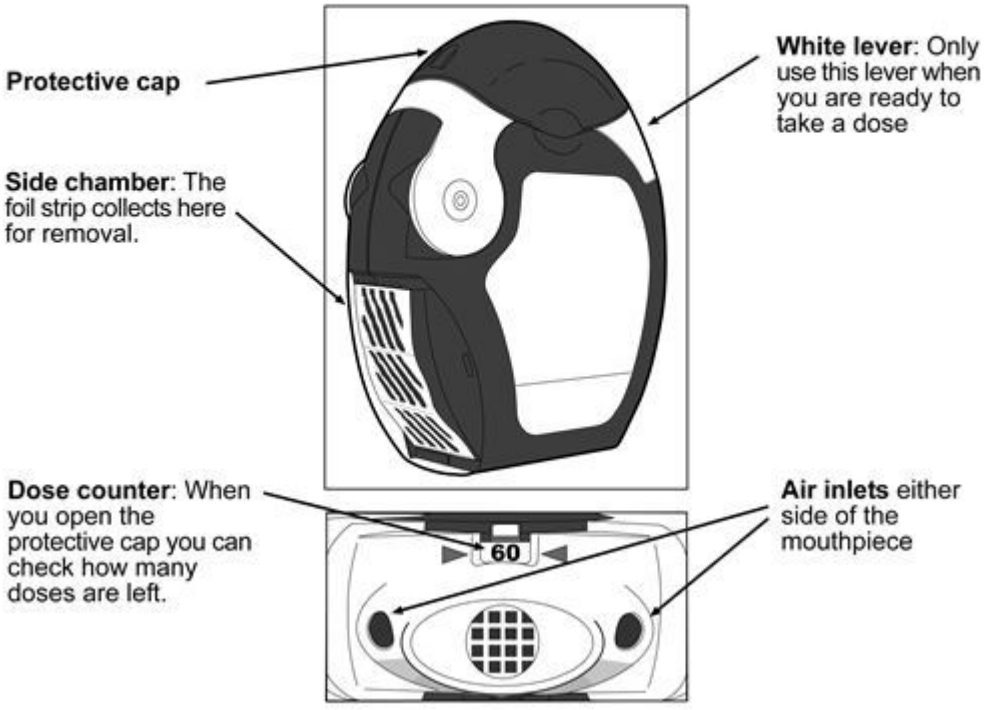
Special populations:
There are no special dosing requirements for elderly patients. There are no data available for use of AirBuFo Forspiro in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

Method of administration

Instructions for use:
Patients should be demonstrated how to use the Forspiro inhaler and correct use should be checked regularly.

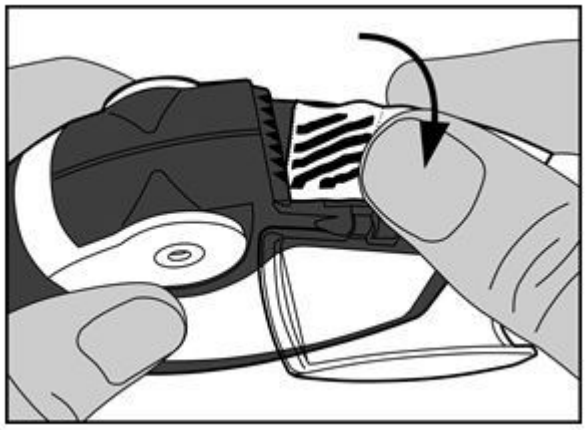
The inhaler contains 60 doses of powder medicinal product in a coiled strip of foil. It has a dose counter which indicates how many doses are left counting down from 60 to 0. When the last 10 doses have been reached the numbers will be on a red background.

The inhaler is not refillable – it should be disposed of when it is empty and be replaced with a new one.



Before using the inhaler

- The transparent side chamber door should be opened.
- The foil strip should be removed from the side chamber by carefully tearing away the full length of strip against the 'teeth' of the side chamber as shown below.The strip should **not be pulled or tugged**.

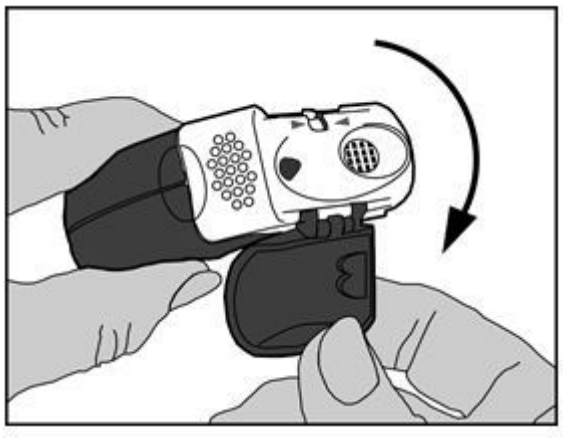


- The side chamber door should be closed and the used strip should be disposed of.

Note: As the inhaler is used the side chamber will gradually fill up with used strip. The foil strips with **black bars don't contain medicinal product**. Eventually the numbered sections of the strip will appear in the side chamber. **There should never be more than 2 sections of foil strip** in the side chamber as they may cause the inhaler to jam. The strip should be torn away carefully as shown above, and disposed of safely.

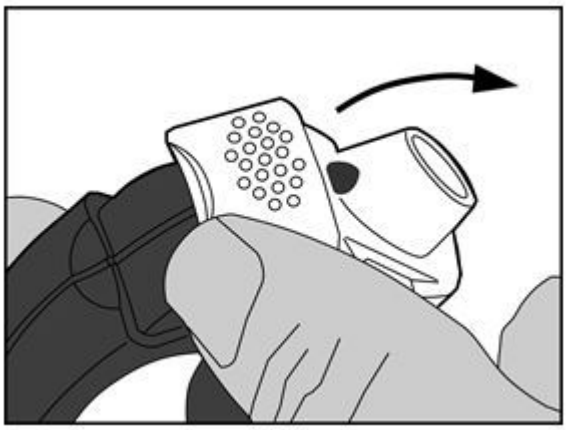
Using the inhaler
The inhaler should be held in hands, as seen in the pictures.

1. Open



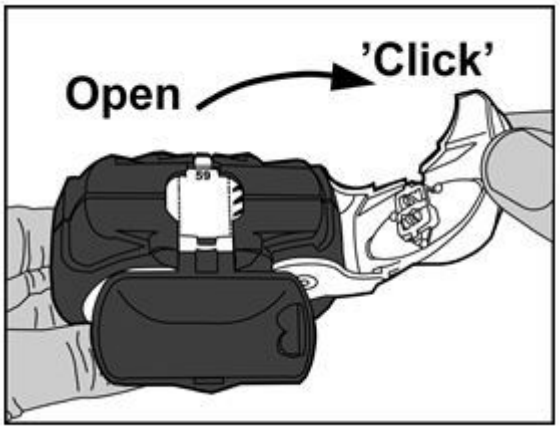
- The protective **cap should be opened downwards** to reveal the mouthpiece.
- The dose counter should be checked to see how many doses are left.

2. Preparation of the dose

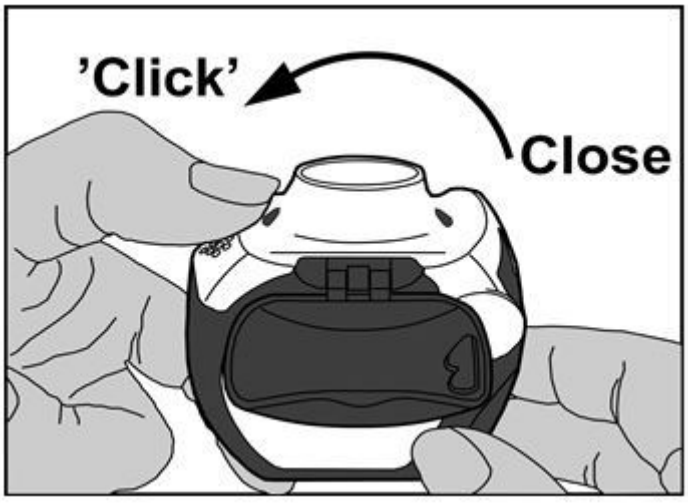


- The edge of the **white lever should be lifted up**. The side chamber should be closed.

Note: The white lever should only be operated when the patient is ready to inhale a dose of the medicinal product. If the patient plays with the white lever he/she will waste doses.



- **Open:** The **white lever should be moved over fully**as far as it will go and **until it clicks**. This action moves a new dose into position with the number at the top.



- **Close:** Afterwards the **white lever should be closed fully**so that it **clicks**back into its original position. The inhaler is now ready for immediate use.

3. Inhalation of the dose

- Away from the inhaler mouthpiece, the patient should breathe out as much as is comfortable**.** It should **never be breathed directly into** the inhaler as this could affect the dose.
- The inhaler should be hold level with the **protective cap pointing downwards**.
- The lips should be closed firmly around the mouthpiece.
- The patient should breathe in as deeply and as hard as possible through the inhaler, not through the nose.

- The inhaler should be removed from the mouth and the **breath should be held for 5-10 seconds** or as long as is possible without causing discomfort.
- Afterwards, the patient should breathe out slowly, **but not into the inhaler**.
- The protective cap should be closed over the mouthpiece.
- The mouth should be rinsed with water, which should be spat out afterwards. This may help to prevent getting fungal infection in the mouth and becoming hoarse.

Cleaning

- The outside of the mouthpiece should be wiped with a clean, dry tissue if necessary.
- The inhaler should not be taken apart to clean it or for any other purpose!
- The inhaler parts must not be cleaned with water or wet wipes as dampness can affect the dose!
- Pins or other sharp objects must never be inserted into the mouthpiece, or any other part, as this may damage the inhaler!

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly.

If patients find the treatment ineffective, or exceed the highest recommended dose of AirBuFo Forspiro, medical attention must be sought (see section 4.2). Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening

and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

Patients should be advised to have their rescue inhaler available at all times, either AirBuFo Forspiro (for asthma patients using AirBuFo Forspiro as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for all patients using AirBuFo Forspiro as maintenance therapy only).

Patients should be reminded to take their AirBuFo Forspiro maintenance dose as prescribed, even when asymptomatic. The prophylactic use of AirBuFo Forspiro, e.g. before exercise, has not been studied. The reliever inhalations of AirBuFo Forspiro should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of AirBuFo Forspiro. Regular review of patients as treatment is stepped down is important. The lowest effective dose of AirBuFo Forspiro should be used (see section 4.2).

Patients should not be initiated on AirBuFo Forspiro during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with AirBuFo Forspiro. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with AirBuFo Forspiro.

There are no clinical study data on budesonide/formoterol available in COPD patients with a pre-bronchodilator FEV_1 >50% predicted normal and with a post-bronchodilator FEV_1 <70% predicted normal (see section 5.1).

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath, after dosing. If the patient experiences paradoxical bronchospasm AirBuFo Forspiro should be discontinued immediately, the patient should be assessed and an alternative therapy instituted, if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway (see section 4.8).

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see section 4.8).

Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. Long-term studies with inhaled budesonide in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of budesonide/formoterol at higher doses is available.

If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to AirBuFo Forspiro therapy.

The benefits of inhaled budesonide therapy would normally minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA axis function should be monitored regularly.

The prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore, additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia.

Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly.

During transfer from oral therapy to AirBuFo Forspiro, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain.

Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

To minimise the risk of oropharyngeal candida infection (see section 4.8), the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible the time interval between administration of the interacting medicinal products should be as long as possible. In patients using potent CYP3A4 inhibitors, AirBuFo Forspiro maintenance and reliever therapy is not recommended.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects.

AirBuFo Forspiro should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

The need for, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

Potentially serious hypokalaemia may result from high doses of β_2 adrenoceptor agonists. Concomitant treatment of β_2 adrenoceptor agonists with medicinal products which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the β_2 adrenoceptor agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances.

As for all β_2 adrenoceptor agonists, additional blood glucose controls should be considered in diabetic patients.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

AirBuFo Forspiro contains lactose monohydrate (4.4 mg/inhalation). This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist.

Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

Pneumonia in patients with COPD
An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, cobicistat and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible (section 4.4). In patients using potent CYP3A4 inhibitors, AirBuFo Forspiro maintenance and reliever therapy is not recommended.

The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose of 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increase in plasma levels (on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

Pharmacodynamic interactions
Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. AirBuFo Forspiro should therefore not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons.

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine) and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2 sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Concomitant use of other beta-adrenergic or anticholinergic medicinal products can have a potentially additive bronchodilating effect.

Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Hypokalaemia may result from beta2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics (see section 4.4).

Budesonide and formoterol have not been observed to interact with any other medicinal products used in the treatment of asthma.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
For budesonide/formoterol or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-foetal development study in the rat, showed no evidence of any additional effect from the combination.

There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse reactions in reproduction studies at very high systemic exposure levels (see section 5.3).

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticoids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

During pregnancy, AirBuFo Forspiro should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

Breast-feeding
Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of AirBuFo Forspiro to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility
There is no data available on the potential effect of budesonide on fertility. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure (see section 5.3).

4.7 Effects on ability to drive and use machines

AirBuFo Forspiro has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Since AirBuFo Forspiro contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common related adverse drug reactions are pharmacologically predictable side-effects of β_2 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.

Adverse reactions which have been associated with budesonide or formoterol are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Frequencies were derived from clinical trial data. The incidence in placebo was not taken into account.

Table 1

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	Candida infections in the oropharynx Pneumonia (in COPD patients)
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing's syndrome Adrenal suppression Growth retardation Decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Aggression Psychomotor hyperactivity Anxiety Sleep disorders
	Very rare	Depression Behavioural changes (predominantly in children)
Nervous system disorders	Common	Headache Tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Eye disorders	Uncommon	Blurred vision (see also section 4.4)
	Very rare	Cataract and glaucoma
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris Prolongation of QTc-interval
Vascular disorders	Very rare	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat Coughing Dysphonia including hoarseness
	Rare	Bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps

Candida infection in the oropharynx is due to medicinal product deposition. Advising the patient to rinse the mouth out with water after each maintenance dose will minimize the risk. Oropharyngeal Candida infection usually responds to topical antifungal treatment without the need to discontinue the inhaled corticosteroid. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

As with other inhalation therapy, paradoxical bronchospasm may occur very rarely, affecting less than 1 in 10,000 people, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. AirBuFo Forspiro should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary (see section 4.4).

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity.

Treatment with β_2 adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Paediatric population
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; website: www.hpra.ie

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β_2 adrenoceptor agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdose with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticoid effects, such as hypercorticism and adrenal suppression, may appear.

If AirBuFo Forspiro therapy has to be withdrawn due to overdose of the formoterol component of the medicinal product, provision of appropriate inhaled corticosteroid therapy must be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases: Adrenergics, Inhalants
ATC-code: R03AK07

Mechanisms of action and Pharmacodynamic effects
This medicinal product contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The specific properties of budesonide and formoterol allow the combination to be used either as maintenance and reliever therapy or as maintenance treatment of asthma.

Budesonide
Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse reactions than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Formoterol
Formoterol is a selective β_2 adrenoceptor agonist that, when inhaled, results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy and safety

Asthma

Clinical efficacy for budesonide/formoterol maintenance therapy
Clinical studies in adults have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. In two 12-week studies the effect on lung function of budesonide/formoterol was equal to that of the free combination of budesonide and formoterol, and exceeded that of budesonide alone. All treatment arms used a short-acting β_2 adrenoceptor agonist as needed. There was no sign of attenuation of the antiasthmatic effect over time.

Two 12-week paediatric studies have been performed in which 265 children aged 6-11 years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80 micrograms /4.5 micrograms/inhalation twice daily), and a short acting β_2 adrenoceptor agonist as needed. In both studies, lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide alone.

Clinical efficacy for budesonide/formoterol maintenance and reliever therapy
A total of 12,076 asthma patients were included in 5 double-blind efficacy and safety studies (4,447 were randomised to budesonide/formoterol maintenance and reliever therapy) for 6 or 12 months. Patients were required to be symptomatic despite use of inhaled glucocorticosteroids.

Budesonide/formoterol maintenance and reliever therapy provided statistically significant and clinically meaningful reductions in severe exacerbations for all comparisons in all 5 studies. This included a comparison with budesonide/formoterol at a higher maintenance dose with terbutaline as reliever (study 735) and budesonide/formoterol at the same maintenance dose with either formoterol or terbutaline as reliever (study 734) (Table 2). In Study 735, lung function, symptom control, and reliever use were similar in all treatment groups. In Study 734, symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments. In the 5 studies combined, patients receiving budesonide/formoterol maintenance and reliever therapy used, on average, no reliever inhalations on 57% of treatment days. There was no sign of development of tolerance over time.

Table 2 Overview of severe exacerbations in clinical studies.

Study No. Duration	**Treatment groups**	**n**	**Severe exacerbations[a]**	
			Events	**Events/ patients-year**
Study 735 6 months	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1,103**	**125**	**0.23[b]**
	Budesonide/formoterol 320/9 µg bd + terbutaline 0.4 mg as needed	1,099	173	0.32
	Salmeterol/fluticasone 2 x 25/125 µg bd + terbutaline 0.4 mg as needed	1,119	208	0.38
Study 734 12 months	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1,107**	**194**	**0.19 [b]**
	Budesonide/formoterol 160/4.5 µg bd + formoterol 4.5 µg as needed	1,137	296	0.29
	Budesonide/formoterol 160/4.5 µg bd + terbutaline 0.4 mg as needed	1,138	377	0.37

a Hospitalisation/emergency room treatment or treatment with oral steroids.
b Reduction in exacerbation rate is statistically significant (P value <0.01) for both comparisons.

Comparable efficacy and safety in adolescents and adults was demonstrated in 6 double-blind studies, comprising the 5 studies mentioned above and an additional study using a higher maintenance dose of 160/4.5 micrograms, two inhalations twice daily. These assessments were based on a total of 14,385 asthma patients of whom 1,847 were adolescents. The number of adolescent patients taking more than 8 inhalations on at least one day as part of budesonide/formoterol maintenance and reliever therapy was limited, and such use was infrequent.

In 2 other studies with patients seeking medical attention due to acute asthma symptoms, budesonide/formoterol provided rapid and effective relief of bronchoconstriction similar to salbutamol and formoterol.

COPD

In two 12-month studies, the effect on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with moderate to severe COPD was evaluated. The inclusion criteria for both studies was pre-bronchodilator FEV_1 <50% predicted normal. Median post-bronchodilator FEV_1 at inclusion in the trials was 42% predicted normal.

The mean number of exacerbations per year (as defined above) was significantly reduced with budesonide/formoterol as compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8-1.9 in the placebo/formoterol group). The mean number of days on oral corticosteroids/patient during the 12 months was slightly reduced in the budesonide/formoterol group (7-8 days/patient/year compared with 11-12 and 9-12 days in the placebo and formoterol groups, respectively). For changes in lung-function parameters, such as FEV_1, budesonide/formoterol was not superior to treatment with formoterol alone.

5.2 Pharmacokinetic properties

Absorption

The fixed-dose combination of budesonide and formoterol, and the corresponding mono-products have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively. In spite of this, a small increase in cortisol suppression was seen after administration of the fixed-dose combination compared to the mono-products. The difference is considered not to have an impact on clinical safety.

There was no evidence of pharmacokinetic interactions between budesonide and formoterol.

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as the fixed-dose combination. For budesonide, AUC was slightly higher, rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. For formoterol, maximal plasma concentration was similar after administration of the fixed combination. Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, mean lung deposition of budesonide after inhalation via the powder inhaler ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose. In children 6-16 years of age the lung deposition falls in the same range as in adults for the same given dose. The resulting plasma concentrations were not determined.

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies the mean lung deposition of formoterol after inhalation via the powder inhaler ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

Distribution and biotransformation

Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 l/kg for formoterol and 3 l/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-betahydroxy-budesonide and 16-alfa-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

Elimination

The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation, 8% to 13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 l/min) and the terminal elimination half-life averages 17 hours.

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are eliminated in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 l/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.
The pharmacokinetics of budesonide or formoterol in patients with renal failure are unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

Linearity/non-linearity

Systemic exposure for both budesonide and formoterol correlates in a linear fashion to administered dose.

5.3 Preclinical safety data

The toxicity observed in animal studies with budesonide and formoterol, given in combination or separately, were effects associated with exaggerated pharmacological activity.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended doses. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results do not seem to be relevant in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (contains milk proteins)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

A red/white coloured plastic inhaler containing an OPA/Al/PVC-Al blister with 60 pre-metered doses of inhalation powder.

Pack sizes: 1, 2 or 6 inhaler(s), each with 60 doses.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/284/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th May 2018
Date of last renewal: 12th April 2023

10 DATE OF REVISION OF THE TEXT

May 2023