SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FORALIN 200 Inhaler.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose that leaves the mouthpiece) contains:
budesonide 160 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation.

Each metered dose contains: budesonide 200 micrograms/inhalation and formoterol fumarate dihydrate 6 micrograms/inhalation.

Excipient with known effect
Lactose monohydrate 730 micrograms per delivered dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder.

White powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FORALIN 200 Inhaler 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.

FORALIN 200 Inhaler is also indicated as reliever therapy for adults and adolescents (12 years and older) with mild asthma.

Chronic Obstructive Pulmonary Disease (COPD)
FORALIN 200 Inhaler 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
The dosage of the components of FORALIN 200 Inhaler 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. It is recommended that all patients with asthma are provided with a written personal asthma action plan. If an individual patient should require a combination of doses other than those 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 usage of formalin remains optimal. When a new treatment is initiated or treatment dose adjusted, patients should be assessed more frequently. For Foralin there are three treatment approaches:

A. Foralin maintenance therapy: Foralin is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue.

B. Foralin maintenance and reliever therapy: Foralin is taken as regular maintenance treatment and as needed in response to symptoms.

C. Foralin reliever therapy: Foralin is taken as needed in response to symptoms.

A. FORALIN 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 Foralin 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 (6 years and older): A lower strength
(100 micrograms/6 micrograms/inhalation) is available for children 6-11 years.

Children under 6 years: As only limited data are available, Foralin is not recommended for children younger than 6 years.

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

For patients taking Foralin as reliever, preventative use of Foralin for allergenor exercise-induced bronchoconstriction should be discussed between physician and patient; the recommended use should take into consideration the frequency of need. In case of frequent need of bronchodilation without corresponding need for an increased dose of inhaled corticosteroids, an alternative reliever should be used.

Foralin maintenance and reliever therapy should especially be considered for patients with:

- inadequate asthma control and in frequent need of reliever medication
- asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Foralin 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: Foralin maintenance and reliever therapy is not recommended for children.

C. Foralin reliever therapy

Mild asthma patients take Foralin as needed in response to symptoms. This will provide relief by the rapid acting bronchodilation and also reduce inflammation. Patients should be advised to always have Foralin available for rescue use.

For patients taking Foralin as reliever, preventative use of Foralin for allergenor exercise-induced bronchoconstriction should be discussed between physician and patient; the recommended use should take into consideration the frequency of need. In case of frequent need of bronchodilation without corresponding need for an increased dose of inhaled corticosteroids, an alternative reliever should be used.

Recommended doses:
Adults and adolescents (12 years and older): Patients should take 1 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.

If a patient finds the treatment less effective or experiences progressive deterioration of symptoms despite taking Foralin as needed the patient should seek medical attention as soon as possible (see section 4.4).

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 reassessed for alternative explanations of persisting symptoms. Patients should be assessed at regular intervals according to local practice to determine whether their as-needed treatment with Foralin remains optimal or whether regular scheduled treatment with inhaled corticosteroid-containing maintenance medication should be initiated.

Children under 12 years: Foralin reliever therapy is not recommended for children.

COPD
Recommended doses:
Adults: 2 inhalations twice daily

General information
Special patient groups:
There are no special dosing requirements for elderly patients. There are no data available for use of Foralin 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 correct use of Foralin Inhaler
The inhaler is inspiratory flow-driven, which means that when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient

- to carefully read the instructions for use in the patient information leaflet which is packed together with each Foralin Inhaler
- to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs.
- never to breathe out through the mouthpiece.
- to replace the cover of the Foralin Inhaler after use.
- to rinse their mouth out with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

The patient may not taste or feel any medication when using Foralin inhaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 (lactose, which contains small amounts of milk proteins).

4.4 Special warnings and precautions for use

Dosing advice
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Foralin. Regular review of patients as

treatment is stepped down is important. The lowest effective dose of Foralin should be used (see section 4.2).

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

If patients take Foralin as maintenance (therapy A or B), they should be reminded to take their Foralin maintenance dose as prescribed, even when asymptomatic.

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.

It is recommended that the maintenance dose is tapered when the treatment is discontinued and the dosing should not be stopped abruptly. Complete withdrawal of inhaled corticosteroids should not be considered unless it is temporarily required to confirm diagnosis of asthma.

Deterioration of disease

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

If patients find the treatment less effective, or need more inhalations than usual, 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 not be initiated on Foralin during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Transfer from oral therapy

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 Foralin 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.

During transfer from oral therapy to Foralin, 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.

Excipients

Foralin Inhaler contains lactose monohydrate (<1 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.

Interactions with other medicinal products

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 drugs should be as long as possible. In patients using potent CYP3A4 inhibitors, Foralin maintenance and reliever therapy is not recommended.

Caution with special diseases

Foralin 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 QTcinterval. Formoterol itself may induce prolongation of the QTc-interval.

Potentially serious hypokalaemia may result from high doses of β_2 adrenoceptor agonists. Concomitant treatment of β_2 adrenoceptor agonists with drugs 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.

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.

Systemic effects

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 coexisting 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 Foralin at higher doses is available.

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.

Adrenal function

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

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 hypoglycemia.

Paradoxical bronchospasm
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 Foralin 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).

Pediatric 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.

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

An increase in the incidence of pneumonia, including pneumonia requiring hospitalization, 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 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, Foralin 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. Foralin 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 QTcinterval 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 drugs or anticholinergic drugs 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 β_2-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 drugs used in the treatment of asthma.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
For Foralin 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 effects 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 glucocorticosteroids 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, Foralin 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.

Breastfeeding

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 Foralin 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

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

4.8 Undesirable effects

Since Foralin 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 drug related adverse 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 (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000) and very rare (<1/10 000).

Table 1

SOC	**Frequency**	**Adverse Drug 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	Vision blurred (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 drug deposition. Advising the patient to rinse the mouth out with water after each maintenance dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal 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. Foralin 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.

<u>Paediatric population</u>

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 the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

If Foralin t therapy has to be withdrawn due to overdose of the formoterol component of the drug, 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
Foralin 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 both as an anti-inflammatory reliever and as maintenance treatment of asthma.

Budesonide
Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent antiinflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse effects 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
Budesonide/formoterol maintenance therapy (Therapy A in Section 4.2)
Clinical studies in adults have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. In two 12week 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 (SABA) as needed. There was no sign of attenuation of the anti-asthmatic 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 SABA as needed. In both studies, lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide alone.

Budesonide/formoterol maintenance and reliever therapy (Therapy B in Section 4.2) A total of 12076 asthma patients were included in 5 double-blind efficacy and safety studies (4447 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 (budesonide/formoterol maintenance and reliever therapy)

Study No. Duration	Treatment groups	n	Severe exacerbations[a]	
			Events	Events/ patient-year
Study 735 6 months	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1103**	**125**	**0.23**[b] 0.32
	Budesonide/formoterol 320/9 µg bd + terbutaline 0.4 mg as needed	1099	173	
	Salmeterol/fluticasone 2 x 25/125 µg bd + terbutaline 0.4 mg as needed	1119	208	0.38
Study 734 12 months	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1107**	**194**	**0.19**[b] 0.29
	Budesonide/formoterol 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	
	Budesonide/formoterol 160/4.5 µg bd + terbutaline 0.4 mg as needed	1138	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 were 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 14385 asthma patients of whom 1847 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.

Budesonide/formoterol reliever therapy (Therapy C in Section 4.2)
A total of 8064 adult and adolescent asthma patients with mild asthma were included in 2 randomised, double-blind, double-dummy, placebo-controlled, 52-week efficacy and safety studies (SYGMA 1 and SYGMA 2). Across both studies, 889 patients were adolescents. At study entry, patients were required to be uncontrolled on only short-acting inhaled bronchodilator as needed or controlled on a low dose of inhaled corticosteroids or a leukotriene receptor agonist plus a short-acting inhaled bronchodilator as needed.

A further 1565 adult asthma patients were included in 2 randomised, open-label,
52-week investigator-sponsored efficacy and safety studies (Novel START and PRACTICAL). In Novel START, patients had used as-needed short-acting inhaled bronchodilator (without any other asthma medication) in the 3 months before study entry, while in PRACTICAL, patients had used as-needed short-acting inhaled bronchodilator alone or a low to medium dose of inhaled corticosteroids plus shortacting inhaled bronchodilator as needed at study entry.

Exacerbation rate
The primary endpoint in SYGMA 2 and PRACTICAL was the annual severe exacerbation rate, while the rate of all exacerbations was the primary endpoint in Novel START. The primary endpoint in SYGMA 1 was 'well-controlled asthma weeks' (WCAW), a composite measure of asthma control.

Table 3 summarises the rate of exacerbations by treatment group in the 4 studies. SYGMA 2 showed that the severe exacerbation rate with budesonide/formoterol reliever therapy was comparable to budesonide maintenance treatment plus a shortacting β_2 agonist (SABA) reliever and that this protection against severe exacerbations was achieved with a 75% reduction in median inhaled steroid load. In PRACTICAL, a statistically significant reduction in the severe exacerbation rate was observed with budesonide/formoterol reliever therapy compared with budesonide maintenance treatment plus a SABA reliever. In Novel START, budesonide/formoterol reliever therapy provided a statistically significant reduction in the exacerbation rate compared with a SABA reliever.

Table 3 Overview of asthma exacerbations in clinical studies (budesonide/formoterol reliever therapy)

Study No. Duration Blinding	Treatment groups[a]	n	Exacerbations[b]		Rate ratio (2-sided 95% CI) versus budesonide/ formoterol
			Events	Events/ patient-year	
Severe exacerbations (primary endpoint in SYGMA 2 and PRACTICAL, secondary endpoint in SYGMA 1)					

SYGMA 2 **12 months** **Double blind**	**Placebo bd + budesonide/formoterol 160/4.5 µg as needed**	**2084**	**217**	**0.11**	**NA**
	Budesonide 160 µg bd + terbutaline 0.4 mg as needed	2083	221	0.12	0.97 (0.78, 1.20) p = 0.754[c]
PRACTICAL **12 months**	**Budesonide/formoterol 160/4.5 µg as needed**	**437**	**48**	**0.119**	NA
Open label	Budesonide/formoterol 160/4.5 µg bd + terbutaline 0.4 mg as needed	448	68	0.172	0.69 (0.48, 1.00) p = 0.049
SYGMA 1 **12 months** **Double blind**	**Placebo bd + budesonide/formoterol 160/4.5 µg as needed**	**1277**	**77**	**0.07**	NA
	Placebo bd + terbutaline 0.4 mg as needed	1277	188	0.20	0.36 (0.27, 0.49) p <0.001
	Budesonide 160 µg bd + terbutaline 0.4 mg as needed	1282	89	0.09	0.83 (0.59, 1.16) p = 0.279
All exacerbations (primary endpoint in Novel START)					
Novel START **12 months** **Open label**	**Budesonide/formoterol 160/4.5 µg as needed**	**220**	**37**	**0.195**	NA
	Budesonide 160 µg bd + salbutamol 200 µg as needed	225	32	0.175	1.12 (0.70, 1.79) p = 0.65
	Salbutamol 200 µg as needed	223	74	0.400	0.49 (0.33, 0.72) p <0.001

[a] Budesonide 160 µg (delivered dose) corresponds to budesonide 200 µg (metered dose).

[b] Severe exacerbations were defined as deteriorating asthma requiring treatment with systemic steroids for at least 3 days, or hospital admission or emergency room visit due to asthma requiring systemic steroids. All exacerbations in Novel START were defined as worsening of asthma resulting in an urgent medical review or a prescription of systemic steroids for any duration or high β_2 agonist use.

[c] The upper limit (1.16) of the 1-sided 95% CI for the rate ratio was below the prespecified non-inferiority limit (1.20).

Asthma control

In SYGMA 1, in terms of the WCAW, budesonide/formoterol reliever therapy was superior to a SABA reliever (mean percentage well controlled asthma weeks: 34.4% versus 31.1%, respectively; odds

ratio 1.14 [95% CI 1.00 to 1.30], p-value = 0.046) and was inferior to budesonide maintenance treatment plus a SABA reliever (34.4% versus 44.4% weeks, respectively; odds ratio 0.64 [95% CI 0.57 to 0.73], lower limit of the CI ≥ 0.8 for non-inferiority).

Improvements in asthma control (as defined by ACQ5) in patients using budesonide/formoterol reliever therapy were superior to improvements in patients using a SABA as needed (SYGMA 1: mean difference −0.15, 95% CI −0.20 to −0.11, p-value < 0.001; Novel START: −0.15; 95% CI, −0.24 to −0.06). In the SYGMA studies and Novel START, improvements in asthma control were lower for budesonide/formoterol reliever therapy compared to budesonide maintenance treatment plus a SABA reliever (SYGMA 1: 0.15, 95% CI 0.10 to 0.20; SYGMA 2:
0.11, 95% CI 0.07 to 0.15, both p-values < 0.001; Novel START: 0.14; 95% CI, 0.05 to 0.23) but there was no difference between the groups in PRACTICAL (0.06, 95% CI, −0.005 to 0.12, p =0.07). For all comparisons, the mean difference in treatment effect upon ACQ5 were not clinically meaningful (as assessed by a difference of greater than or equal to 0.5). These results were observed in a clinical study setting with considerably higher adherence to budesonide maintenance dosing than expected in real life.

Lung function
In SYGMA 1, improvements in mean pre-bronchodilator FEV1 compared to baseline were statistically significantly larger for patients on budesonide/formoterol reliever therapy compared to patients using a SABA reliever (53.8 mL; 95% CI 29.1 to 78.5; p <0.001).

In both SYGMA studies, statistically significantly smaller improvements in FEV_1 were observed for budesonide/formoterol reliever therapy compared to budesonide maintenance treatment plus a SABA reliever (SYGMA 1: −54.3 mL; 95% CI −78.8 to −29.8; p <0.001; SYGMA 2: −32.6 mL; 95% CI −53.7 to −11.4; p = 0.003); For both comparisons, the mean differences in treatment effect were small (approximately 30 to 55 mL, equating to approximately 2% of the baseline mean). In Novel START and PRACTICAL, there were no significant differences in FEV_1 versus SABA (Novel START: 0.03 L; 95% CI, −0.006 to 0.07) or versus budesonide maintenance treatment plus a SABA reliever (Novel START: 0.004 L; 95% CI, −0.03 to 0.04; PRACTICAL: 0.006 L; 95% CI −0.026 to 0.04; p = 0·69).

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 monoproducts 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 with the monoproducts. 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-beta-hydroxy-budesonide and 16-alfa-hydroxyprednisolone, 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 children and 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 (which contains milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from frost.

6.5 Nature and contents of container

Primary Pack: 14 ml Aluminium container fitted with a 50 mcl suitable metering valve and a 0.48 mm aerosol actuator with dose counter

Secondary Pack: Carton containing aerosol of 120 MD

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

CIPLA LIMITED
Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg,
Lower Parel, Mumbai 400 013
Country: India

8 MARKETING AUTHORISATION NUMBER(S)

15522

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/07/2014

10 DATES OF REVISION OF THE TEXT

30/03/2026