Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Symbidow DPI Capsule 200/6 microgram (Budesonide + Formoterol) 200 micrograms/6 micrograms

2. Qualitative and quantitative composition

Each capsule contains:
Budesonide.....200 mcg
Formoterol fumarate dihydrate .....6 mcg

The product contains 24.794 mg of Lactose Monohydrate
For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Hard capsule (inhalation powder)
Visual description: Light Green cap and transparent body, Hypromellose capsule size No. 3 containing white to off white powder.

4. Clinical particulars

4.1 Therapeutic indications

Symbidow 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 β2 adrenoceptor agonist) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists.
Or
- patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.

Chronic Obstructive Pulmonary Disease (COPD)

Symbidow is indicated in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV1) <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

Asthma
Symbidow is not intended for the initial management of asthma. The dosage of the components of Budesonide+Formoterol 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 those available in the combination inhaler, appropriate doses of β2 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 dosage of Budesonide+Formoterol remains optimal. When long-term control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

For Symbidow 200mcg/6mcg there are two treatment approaches:

<u>Symbidow 200mcg/6mcg maintenance therapy</u>
Symbidow is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue.
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 Budesonide+Formoterol 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.

<u>Symbidow 200mcg/6mcg maintenance and reliever therapy</u>

Symbidow is taken as regular maintenance treatment and as needed in response to symptoms.
Patients take a daily maintenance dose of Symbidow (200mcg/6mcg) and in addition take Symbidow as needed in response to symptoms. Patients should be advised to always have Symbidow available for rescue use.
Symbidow 200mcg/6mcg 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 Budesonide+Formoterol 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 re-assessed, and their maintenance therapy should be reconsidered.

- Children under 12 years: Symbidow maintenance and reliever therapy is not recommended for children.

<u>COPD</u>

Symbidow 200mcg/6mcg Recommended doses:

Adults: 2 inhalations twice daily

General information for Special patient groups:
There are no special dosing requirements for elderly patients. There are no data available for use of Symbidow 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.
<u>Method of administration</u>
Instructions for correct use of Symbidow:
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 Symbidow 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 Symbidow 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 Symbidow inhaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity to the active substances or to the excipient listed in section 6.1 (lactose, which contains small amounts of milk proteins).

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 Budesonide+Formoterol, 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 Budesonide+Formoterol (for asthma patients using Budesonide+Formoterol as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for all patients using Budesonide+Formoterol as maintenance therapy only).

Patients should be reminded to take their Budesonide+Formoterol maintenance dose as prescribed, even when asymptomatic. The prophylactic use of Budesonide+Formoterol, e.g. before exercise, has not been studied. The reliever inhalations of Budesonide+Formoterol 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 Budesonide+Formoterol. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Budesonide+Formoterol should be used (see section 4.2).

Patients should not be initiated on Budesonide+Formoterol, 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 Budesonide+Formoterol. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with Budesonide+Formoterol.

There are no clinical study data on Budesonide + Formoterol, available in COPD patients with a pre- bronchodilator FEV1 >50% predicted normal and with a post-bronchodilator FEV1 <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, Budesonide+Formoterol 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 Budesonide+Formoterol 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 Budesonide+Formoterol, 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 glucocorticosteroid 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 drugs should be as long as possible. In patients using potent CYP3A4 inhibitors, Budesonide+Formoterol maintenance and reliever therapy is not recommended.

Budesonide+Formoterol should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic sub-valvular 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 β2 adrenoceptor agonists. Concomitant treatment of β2 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 β2 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 β2 adrenoceptor agonists, additional blood glucose controls should be considered in diabetic patients.

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 c Budesonide+Formoterol 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.

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 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, Budesonide+Formoterol 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. Budesonide+Formoterol 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 β2 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 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 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 Budesonide+Formoterol combination 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 glucocorticosteroid 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, Budesonide+Formoterol 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.

Lactation

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 Budesonide+Formoterol 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.

Budesonide+Formoterol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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)

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 ofQTc-interval
Vascular disorders	Very rare	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, hoarseness
	Rare	Bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissuedisorders	Uncommon	Bruises
Musculoskeletal and connectivetissue 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 dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid.

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. Budesonide+Formoterol 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 β2 adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β2 adrenoceptor agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting.

Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms of formoterol 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 Budesonide+Formoterol 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
Mechanism of action
Symbidow contains formoterol and budesonide, which have different modes of action and showadditive effects in terms of reduction of COPD exacerbations.

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

Formoterol
Formoterol is a selective β2-adrenoceptor agonist which when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with airway 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.

5.2 Pharmacokinetic properties

Absorption

Following administration of Budesonide+Formoterol 160 micrograms /4.5 micrograms (two or four inhalations twice daily) for 5 days in healthy individuals, plasma concentration of budesonide generally known to be increased in proportion to dose. There is no evidence of pharmacokinetic interactions between budesonide and formoterol.

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 known to be inactivated via conjugation reactions (active O demethylated and de-formylated metabolites are known to be formed, but they are known 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-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 known to be transformed by liver metabolism followed by renal elimination. After inhalation, 8% to 13% of the delivered dose of formoterol is known to be excreted unmetabolized 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 known to be eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are known to be eliminated in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide are known 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 is unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility
Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage *in vitro* and did not exhibit clastogenic potential *in vivo* in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

6. Pharmaceutical particulars

6.1 List of excipients
Lactose monohydrate (Respitose SV003)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months.

6.4 Special precautions for storage:
Store below 30 °C, protected from heat, moisture and light.
Do Not Freeze

6.5 Nature and contents of container

Symbidow is supplied in the following dosage form, strength and pack size: DPI Capsule 200mcg+6mcg 30's

6.6 Special precautions for disposal and other handling:

The inhaler provided with each new prescription should be used. The inhaler in each pack should be disposed of after all capsules in that pack have been used.

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

Instructions for handling and use
Do not swallow Symbidow capsules. Follow the stepwise instruction for use:

1. Pull off inhaler cap and hold the base of the inhaler firmly and tilt the mouthpiece to open the inhaler.

2. Separate 1 of the blisters from the blister card by tearing along the perforation. Take 1 blister and peel away the protective backing to expose the capsule.
3. With dry hands, remove 1 capsule from the blister and place the capsule into the capsule chamber.
4. Close the inhaler fully. You should hear a 'click' as it fully closes.
5. Hold the inhaler upright with the mouthpiece pointing up. Press both piercing buttons together firmly at the same time. You should hear a 'click' as the capsule is being pierced. Release the piercing buttons fully.
6. Before placing the mouthpiece in your mouth, breathe out fully. Do not blow into the mouthpiece.
7. Hold the inhaler. Make sure that the piercing buttons are to the left and right of the inhaler (not up and down). Place the mouthpiece in your mouth and close your lips firmly around the mouthpiece.

   Breathe in rapidly but steadily, as deeply as you can. Do not press the piercing buttons.

8. As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. If you do not hear a whirring noise, the capsule may be stuck in the capsule chamber. If this occurs, open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the piercing buttons to loosen the capsule.
9. Continue to hold your breath for at least 5 to 10 seconds or as long as comfortably possible while removing the inhaler from your mouth, then breathe out.
10. Open the inhaler to see if any powder is left in the capsule. If there is powder left in the capsule, close the inhaler and again place into your mouth to breath.
11. After you have finished taking your dose of Symbidow dry powder inhaler, open the mouthpiece again, remove the empty capsule by tipping it out of the capsule chamber, and throwing it away. Close the inhaler and replace the cap.

    Do not leave the used capsules in the dry powder inhaler

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Martin Dow Limited, lot No. 37, Sector 19, Korangi Industrial Area, Karachi-74900, Pakistan

Manufacturing site address:

Martin Dow Limited, lot No. 37, Sector 19, Korangi Industrial Area, Karachi-74900, Pakistan

8. Marketing authorization number
CTD 9604

9. Date of first registration
06/03/2023

10. Date of revision of the text:
13/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable