SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Foradil® capsules for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 12 micrograms formoterol fumarate dihydrate.

Excipient(s) with known effect:
Each capsule contains 25 mg lactose (as the monohydrate).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Powder For Inhalation, capsules
Clear capsules containing a white powder, with "GC" printed on cap and "FXF" on body or "FXF" on cap and "GC" on body in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Foradil is indicated in asthma (including nocturnal asthma and exercise-induced symptoms) in those treated with inhaled corticosteroids who also require a long-acting beta agonist in accordance with current treatment guidelines.

Prophylaxis and treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

4.2 Posology and method of administration

Posology
For use in adults and in children 6 years of age and older

Adults

Asthma
Foradil should only be prescribed as an add-on to an inhaled corticosteroid.

Regular maintenance therapy:

1 to 2 inhalation capsules (equivalent to 12 to 24 micrograms formoterol) twice daily. Foradil should only be prescribed as an add-on to an inhaled corticosteroid (ICS).
If required, an additional 1 to 2 capsules per day may be used for the relief of ordinary symptoms provided the recommended daily maximum dose of 48 micrograms per day is not exceeded. However, if the need for additional doses is more than occasional (e.g. more

frequent than 2 days per week) medical advice should be sought and therapy reassessed, as this may indicate a worsening of the underlying condition.
The recommended maximum maintenance dose is 48 micrograms per day.

Foradil should not be used to relieve the acute symptoms of an asthma attack. In the event of an acute attack, a short-acting beta2-agonist should be used (see Section 4.4).

Prophylaxis against exercise-induced bronchospasm

The content of 1 inhalation capsule (12 microgram) should be inhaled at least 15 minutes prior to exercise. In patients with a history of severe bronchospasm, 2 inhalation capsules (24 microgram) may be necessary as prophylaxis.

In patients with persistent asthma, use of Foradil for the prevention of exercise-induced bronchospasm may be clinically indicated, but the treatment of asthma should also include an ICS.

Chronic Obstructive Pulmonary Disease
For regular maintenance therapy, 1 inhalation capsule (equivalent to 12 micrograms נה, formoterol fumarate dihydrate) to be inhaled twice daily.

Children aged 6 years and above

Asthma
Foradil should only be prescribed as an add-on to an inhaled corticosteroid.

For regular maintenance therapy: 1 inhalation capsule (equivalent to 12 micrograms formoterol fumarate dihydrate) to be inhaled twice daily.

The recommended maximum daily dose is 24 micrograms per day.

For children 6-12 years of age, when treatment with an inhaled corticosteroid and long-acting beta2-agonist (LABA) is required, it is recommended to use a combination product, except in cases where separate inhaled corticosteroid and long-acting beta2-agonist inhalers are more appropriate (see Section 4.4).

Although Foradil has a rapid onset of action, current asthma management guidelines recommend that long-acting inhaled bronchodilators should be used for maintenance bronchodilator therapy. They further recommend that in the event of an acute attack, a beta - agonist with a short duration of action should be used.
(see Section 4.4).

In accordance with the current management guidelines, long-acting beta 2-agonists may be added to the treatment regimen in patients experiencing problems with high dose inhaled steroids. Alternatively, where regular symptomatic treatment of asthma is required in addition to inhaled steroids, then long-acting beta 2-agonists can be used. Patients should be advised not to stop or change their steroid therapy when Foradil is introduced.

If the symptoms persist or worsen, or if the recommended dose of Foradil fails to control symptoms (maintain effective relief), this is usually an indication of a worsening of the underlying condition.

Prophylaxis against exercise-induced bronchospasm

The content of 1 inhalation capsule (12 micrograms) should be inhaled at least 15 minutes prior to exercise.

In patients with persistent asthma, use of Foradil for the prevention of exercise-induced bronchospasm may be clinically indicated, but the treatment of asthma should also include an ICS.

Foradil is not recommended in children under 6 years of age.

Children under 6 years

Foradil is not recommended in children under the age of 6 years

Adults and children aged 6 years or older

The bronchodilator effect of Foradil is still significant 12 hours after inhalation. Therefore, in most cases, twice-daily maintenance therapy will control the bronchoconstriction associated with chronic conditions, both during the day and at night.

Special populations

Renal impairment

Formoterol has not been studied in patients with renal impairment.

Hepatic impairment

Formoterol has not been studied in patients with hepatic impairment.

Elderly Patients (older than 65 years)

The pharmacokinetics of Foradil has not been studied in the elderly population. The available data from clinical trials performed in elderly patients do not suggest that the dosage should be different than in other adults.

Method of administration

Foradil capsules for inhalation should be used only with the Aerolizer® inhaler provided in the Foradil pack.

To ensure proper administration of the drug, a physician or other health professional should:

- Show the patient how to use the inhaler.
- Dispense the capsule only together with the inhaler.
- Instruct the patient that the capsules are only for inhalation use and not to be swallowed (see section 4.4).

Detailed handling instructions are included in the package leaflet.

It is important for the patient to understand that the gelatin capsule might fragment and small pieces of gelatin might reach the mouth or throat after inhalation. The tendency for the capsule to break up is minimised by not piercing the capsule more than once.

The capsule made of edible gelatin is not harmful if ingested.

The capsules should be removed from the blister pack **only immediately** before use.

Instructions for use

1. Pull off the cap from the mouthpiece of the inhaler
2. Hold the base of the inhaler firmly and turn the mouthpiece in the direction of the arrow on the bottom of the mouthpiece to open.
3. Take one of the capsules out of the blister strip for the appropriate day. Place it in the capsule shaped compartment in the base of the inhaler. It is important that the capsule is removed from the blister pack **only** immediately before use.
4. Twist the mouthpiece to the closed position until it clicks.
5. Keeping the inhaler upright, firmly squeeze the two blue buttons **once only**. This will pierce the capsule. Release the buttons. Although the capsule is now pierced, the powder will not be released.
6. The patient should breathe out fully.
7. The patient should place the mouthpiece in the mouth and tilt their head slightly back. The lips should be placed around the mouthpiece and the patient should inhale as quickly and as deeply as is possible. As the patient breathes in, the medicine will be inhaled into the lungs.
8. The capsule should be heard spinning in the inhaler. If the whirring noise is not heard, the capsule may be stuck in the compartment. If this occurs, open the inhaler and loosen the capsule by prising it out of the compartment. **Do not** try to loosen the capsule by repeatedly pressing the buttons.
9. If the whirring noise has been heard the patient should hold their **breath** for as long as they comfortably can while taking the inhaler out of the mouth. Then the patient should breathe normally. The inhaler should be opened to see if any powder is still in the capsule. If there is still powder in the capsule steps 6 to 8 should be repeated.
10. After use, the empty capsule should be tipped out and the mouthpiece closed.
11. Replace the cap.
12. If the inhaler needs to be cleaned, wipe the mouthpiece and capsule compartment with a **dry** cloth **or** a clean soft brush.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1

4.4 Special warnings and special precautions for use

Asthma-related death
Formoterol fumarate dihydrate, the active ingredient of Foradil, belongs to the class of long-acting beta2-adrenergic agonists (LABAs). In a study with salmeterol, a different long-acting beta2-agonist, a higher rate of death due to asthma was observed in the patients treated with salmeterol (13/13,176) than in the placebo group (3/13,179). No study adequate to determine whether the rate of asthma-related death is increased with Foradil has been conducted.

In the treatment of asthma
Foradil should not be used (and is not sufficient) as the first treatment for asthma.

When treating patients with asthma, use Foradil only as an add-on to an inhaled corticosteroid (ICS) for patients who are not adequately controlled on an ICS alone or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA.

Children up to the age of 6 years should not be treated with Foradil as sufficient experience is not available for this group. For children 6-12 years of age, when treatment with an ICS and LABA is required, it is recommended to use a combination product, except in cases where a separate ICS and LABA are more appropriate.

Foradil should not be used in conjunction with another LABA

Whenever Foradil is prescribed, patients should be evaluated for the adequacy of the anti-inflammatory therapy they receive. Patients must be advised to continue taking anti-inflammatory therapy unchanged after the introduction of Foradil, even when their symptoms improve.

The daily dose of Foradil should not be increased beyond the maximum recommended dose (see Section 4.2).

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Foradil. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Foradil should be used.

Serious asthma-related adverse events and exacerbations may occur during treatment with Foradil. Clinical studies with Foradil suggested a higher incidence of serious asthma exacerbations in patients who received Foradil than in those who received placebo, particularly in patients 5-12 years of age (see Section 5.1). These studies do not allow precise quantification of the differences in serious asthma exacerbation rates between treatment groups.

Patients should be advised that if, after initiation of Foradil, their symptoms persist, or if the number of doses of Foradil required to control their symptoms increases, this usually indicates a worsening of the underlying condition. In these circumstances, they should be advised to continue treatment but to seek medical advice as soon as possible.

Patients should not be initiated on Foradil or the dose increased during an acute severe asthma exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Foradil must not be used to relieve acute asthma symptoms. In the event of an acute attack, a short-acting beta2-agonist should be used. Patients must be informed of the need to seek medical treatment immediately if their asthma deteriorates suddenly.

Concomitant conditions
Special care and supervision, with particular emphasis on dosage limits, is required in patients receiving Foradil when the following conditions may exist:

Ischaemic heart disease, cardiac arrhythmias, especially third degree atrioventricular block, severe cardiac decompensation, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm, phaeochromocytoma, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, or other severe cardiovascular disorders, such as tachyarrhythmias or severe heart failure.

Formoterol may induce prolongation of the QTc-interval. Caution should be observed when treating patients with prolongation of the QTc-interval and in patients treated with drugs affecting the QTc-interval (see section 4.5).

Caution should be used when co-administering theophylline and formoterol in patients with pre-existing cardiac conditions.

Due to the hyperglycaemic effect of β2-stimulants, including formoterol, additional blood glucose controls are recommended in diabetic patients.

Hypokalaemia

Potentially serious hypokalaemia may result from β2-agonist therapy, including formoterol. Particular caution is advised in severe asthma as this effect may be potentiated by hypoxia and concomitant treatment (see Section 4.5). It is recommended that serum potassium levels be monitored in such situations.

Paradoxical bronchospasm
As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy substituted.

Foradil contains lactose monohydrate less than 500 micrograms per delivered dose. This amount does not normally cause problems in lactose intolerant patients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Incorrect route of administration
There have been reports of patients who have mistakenly swallowed Foradil capsules instead of placing the capsules in the inhalation device. The majority of these ingestions were not associated with side effects. Healthcare providers should discuss with the patient how to correctly use Foradil (see section 4.2). If a patient who is prescribed Foradil does not experience breathing improvement, the healthcare provider should ask how the patient is using Foradil.

4.5 Interaction with other medicaments and other forms of interaction

There are no clinical data to support the advice given below, but from consideration of first principles one might expect the following interactions:

Drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistamines, tricyclic antidepressants and erythromycin may be associated with QT-interval prolongation and an increased risk of ventricular arrhythmia (see section 4.4).

Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Foradil and may require titration of the dose.

Administration of Foradil to patients being treated with monoamine oxidase inhibitors, macrolides or tricyclic antidepressants should be performed with caution, since the action of ß2-adrenergic stimulants on the cardiovascular system may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of β2-agonists. Hypokalaemia may increase susceptibility to cardiac arrhythmias (for example, in patients treated with digitalis) (see Section 4.4).

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

The bronchodilating effects of formoterol can be enhanced by anticholinergic drugs.

β-adrenergic blockers may weaken or antagonise the effect of Foradil. Therefore Foradil should not be given together with ß-adrenergic blockers (including eye drops) unless there are compelling reasons for their use.

4.6 Fertility, pregnancy and lactation

Pregnancy
There were no teratogenic effects revealed in animal tests. In animal studies formoterol has caused implantation losses as well as decreased early postnatal survival and birth weight. The effects appeared at considerably higher systemic exposures than those reached during clinical use of formoterol. However, until further experience is gained, Foradil is not recommended for use during pregnancy (particularly at the end of pregnancy or during labour) unless there is no more established alternative. As with any medicine, use during pregnancy should only be considered if the expected benefit to the mother is greater than any risk to the foetus.

Breast feeding
The substance has been detected in the milk of lactating rats, but it is not known whether formoterol passes into human breast milk, therefore mothers using Foradil should refrain from breast feeding their infants.

Fertility
There is no available data on the effect of formoterol on human fertility. No impairment of fertility was observed in studies performed in male and female rats (see section 5.3).

4.7 Ability to drive and use machines

Patients experiencing dizziness or other similar side effects should be advised to refrain from driving or using machines.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked in descending order of frequency, as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, <1/1,000); very rare (< 1/10,000); unknown (frequency cannot be estimated from available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1

Immune system disorders	
Very rare:	Hypersensitivity (including hypotension, angioneurotic oedema)
Rare	Hypersensitivity reactions e.g. bronchospasm, exanthema, urticaria, pruritus
Metabolism and nutrition disorders	
Rare	Hypokalaemia
Very Rare	Hyperglycaemia
Psychiatric disorders	
Uncommon:	Agitation, anxiety, nervousness, restlessness, insomnia
Central Nervous system disorders	
Common:	Headache, tremor
Uncommon:	Dizziness
Very rare:	Dysgeusia

Cardiac disorders	
Common:	Palpitations
Uncommon:	Tachycardia
Rare:	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
Very rare:	Peripheral oedema. Angina pectoris, prolongation of QTc-interval
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Bronchospasm, throat irritation, including paradoxical bronchospasm, acute asthma exacerbation*
Unknown:	Cough**
Skin and subcutaneous tissue disorders	
Unknown:	Rash**
Gastrointestinal disorders	
Uncommon	Dry mouth
Rare:	Nausea
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle cramps, myalgia
Investigations	
Unknown	Increased blood pressure (including hypertension)**
Vascular Disorders	
Very rare	Variations in blood pressure

*The percent of patients with serious asthma exacerbations in clinical studies was higher for Foradil than for placebo, and the biggest numerical imbalance was observed in children 5-12 years old (see Section 4.4 and 5.1).

** These adverse events were reported in patients treated with Foradil during the post-marketing experience.

As with all inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see section 4.4). Treatment with β2-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies. The excipient lactose contains small amounts of milk proteins. These may cause allergic reactions.

Reporting of suspected adverse reactions

Reporting adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation via either a link of "Side Effects Reporting form" located at the Ministry of Health internet site home page, (**http://www.health.gov.il/**) which refer the user to an online adverse reaction reporting form, or by entering the following link: https://sideeffects.health.gov.il .

4.9 Overdose

Symptoms
There is no clinical experience to date on the management of overdose, however, an overdosage of Foradil would be likely to lead to effects that are typical of β2-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia, prolonged QTc-interval, hypertension.

Treatment
Supportive and symptomatic treatment is indicated. Serious cases should be hospitalised.

Use of cardioselective beta-blockers may be considered, but only subject to extreme caution since the use of β-adrenergic blocker medication may provoke bronchospasm.
Serum potassium should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta2-adrenergic agonist, ATC code: R03AC13.

Formoterol is a potent selective β2-adrenergic stimulant. It exerts a bronchodilator effect in patients with reversible airways obstruction. The effect sets in rapidly (within 1-3 minutes) and is still significant 12 hours after inhalation.

In man, Foradil has been shown to be effective in preventing bronchospasm induced by exercise and methacholine.

Formoterol has been studied in the treatment of conditions associated with COPD, and has been shown to improve symptoms and pulmonary function and quality of life. Formoterol acts on the reversible component of the disease.

Serious asthma exacerbations

Placebo-controlled clinical studies of at least 4 weeks treatment duration with Foradil suggested a higher incidence of serious asthma exacerbations in patients who received Foradil than in those who received placebo, particularly in patients 5-12 years of age.

	Placebo	Foradil 12 ug bd	Foradil 24 ug bd	Albuterol
Placebo controlled clinical studies of at least 4 weeks treatment duration.	0.3 %	0.9 % (Foradil 10 - 12 ug bd)	1.9 %	
Combined data from two 12-week double-blind, randomized, placebo-controlled, parallel-group studies. Age ≥12 y n=1095	0.7 % (2/277)	0.4 % (1/275)	3.3 % (9/271)	0.7 % (2/272)
Multi-centre, randomized, parallel-group, double-blind, placebo-controlled 16 week trial. Age ≥12 y n=2085	0.2 % (1/514)	0.6 % (3/527) 0.2 % (1/517) Open label treatment group - 12 ug bd plus up to two additional doses per day	0.4 % (2/527)	
Randomized, placebo-controlled double-blind 52-week trial. Age 5-12 y n=518	0.0 % (0/176)	4.7 % (8/171)	6.4 % (11/171)	

Experience in children aged 5-12 years with asthma
The safety of Foradil 12 microgram twice daily compared to Foradil 24 microgram twice daily and placebo was investigated in one large, multicenter, randomized, double-blind, 52-week clinical trial in 518 children with asthma (ages 5 to 12 years) in need of daily bronchodilators and anti-inflammatory treatment. More children who received Foradil 24 microgram twice daily (11/171, 6.4%) or Foradil 12 microgram twice daily (8/171, 4.7%) than children who received placebo (0/176, 0.0%) experienced serious asthma exacerbations.

5.2 Pharmacokinetic properties

Foradil has a therapeutic dose range of 12 to 24 micrograms b.i.d. Data on the plasma pharmacokinetics of formoterol were collected in healthy volunteers after inhalation of doses higher than the recommended range and in COPD patients after inhalation of therapeutic doses. Urinary excretion of unchanged formoterol, used as an indirect measure of systemic exposure, correlates with plasma drug disposition data. The elimination half-lives calculated for urine and plasma are similar.

Absorption
Following inhalation of a single 120 microgram dose of formoterol fumarate by healthy volunteers, formoterol was rapidly absorbed into plasma, reaching a maximum concentration of 266 pmol/l within 5 minutes of inhalation. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 micrograms b.i.d. the plasma concentrations of formoterol ranged between 11.5 and 25.7 pmol/L and 23.3 and 50.3 pmol/L respectively at 10 minutes, 2 hours and 6 hours post inhalation.

Studies investigating the cumulative urinary excretion of formoterol and/or its (R,R) and (S,S)-enantiomers, after inhalation of dry powder (12-96 micrograms) or aerosol formulations (12-96 micrograms), showed that absorption increased linearly with the dose.

After 12 weeks administration of 12 micrograms or 24 micrograms formoterol powder b.i.d., the urinary excretion of unchanged formoterol increased by 63-73% in adult patients with asthma, by 19-38% in adult patients with COPD and by 18-84% in children, suggesting a modest and self-limiting accumulation of formoterol in plasma after repeated dosing.

As reported for other inhaled drugs, it is likely that about 90% of formoterol administered from an inhaler will be swallowed and then absorbed from the gastrointestinal tract. This means that the pharmacokinetic characteristics of the oral formulation largely apply also to the inhalation powder. When 80 micrograms of ^{3}H-labelled formoterol fumarate was orally administered to two healthy volunteers, at least 65% of the drug was absorbed.

Distribution

The plasma protein binding of formoterol is 61-64% (34% primarily to albumin).
There is no saturation of binding sites in the concentration range reached with therapeutic doses.

Biotransformation

Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation, with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9, and 2A6) of formoterol, and so consequently the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations. The kinetics of formoterol are similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

Elimination

In asthmatic and COPD patients treated for 12 weeks with 12 or 24 micrograms formoterol fumarate b.i.d., approximately 10% and 7% of the dose, respectively, were recovered in the urine as unchanged formoterol. In asthmatic children, approximately 6% of the dose was recovered in the urine as unchanged formoterol after multiple dosing of 12 and 24 micrograms. The (R,R) and (S,S)-enantiomers accounted, respectively, for 40% and 60% of urinary recovery of unchanged formoterol, after single doses (12 to 120 micrograms) in healthy volunteers and after single and repeated doses in asthma patients.

After a single oral dose of ^{3}H-formoterol, 59-62% of the dose was recovered in the urine and 32-34% in the faeces. Renal clearance of formoterol is 150 mL/min.

After inhalation, plasma formoterol kinetics and urinary excretion rate data in healthy volunteers indicate a biphasic elimination, with the terminal elimination half-lives of the (R,R)- and (S,S)-enantiomers being 13.9 and 12.3 hours, respectively.

Approximately 6.4-8% of the dose was recovered in the urine as unchanged formoterol, with the (R,R) and (S,S)-enantiomers contributing 40% and 60% respectively.

5.3 Preclinical safety data

Mutagenicity
Mutagenicity tests covering a broad range of experimental endpoints have been conducted. No genotoxic effects were found in any of the *in vitro* or *in vivo* tests performed.

Carcinogenicity
Two-year studies in rats and mice did not show any carcinogenic potential.
Male mice treated at very high dose levels showed a slightly higher incidence of benign adrenal subcapsular cell tumours, which are considered to reflect alterations in the physiological ageing process.

Two studies in rats, covering different dose ranges, showed an increase in mesovarial leiomyomas. These benign neoplasms are typically associated with long-term treatment of rats at high doses of β2-adrenergic drugs. Increased incidences of ovarian cysts and benign granulosa/theca cell tumours were also seen; β-agonists are known to have effects on the ovary in rats in which are very likely specific to rodents. A few other tumour types noted in the first study using the higher doses were within the incidences of the historical control population, and were not seen in the lower-dose experiment.

None of the tumour incidences were increased to a statistically significant extent at the lowest dose of the second study, a dose leading to a systemic exposure 10 times higher than that expected from the maximum recommended dose of formoterol.

On the basis of these findings and the absence of a mutagenic potential, it is concluded that use of formoterol at therapeutic doses does not present a carcinogenic risk.

Reproductive toxicity
Animal tests have shown no teratogenic effects. Formoterol was evaluated for its effect on fertility and general reproductive performance in sexually mature male and female rats. Reproduction studies in rats revealed no impairment of fertility or effect on early embryonic development at oral doses up to 3 mg/kg (approximately 1200 times the maximum recommended daily inhalation powder dose in human on a mg/m^2 basis).

After oral administration, formoterol was excreted in the milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin and black ink (containing shellac, black iron oxide (CI 77499, E 172), isopropyl alcohol, N-butyl alcohol, propylene glycol, purified water, dehydrated ethanol and ammonium hydroxide 28%), lactose.

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original packaging (protect from moisture).

6.5 Nature and contents of container

Blister aluminum packs of 30, 60 capsules, with an inhaler device in each pack.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. REGISTRATION HOLDER AND IMPORTER

Novartis Israel Ltd.,

POB 7126, Tel Aviv.

8. MARKETING AUTHORISATION NUMBER

101-97-28552

Revised in Apr2021 according to MOHs guidelines