

## FORADILE®

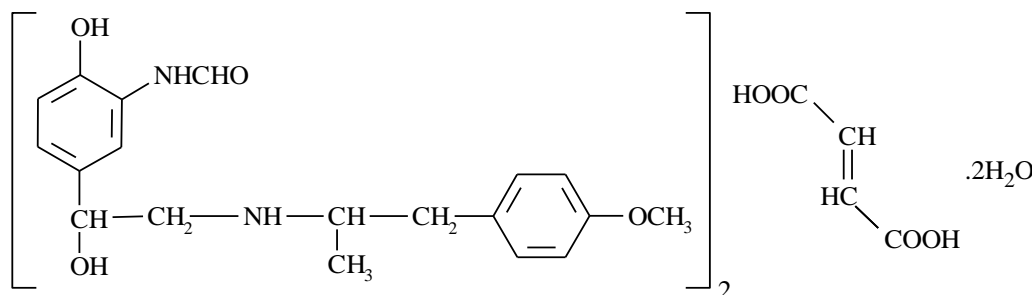
### Eformoterol fumarate dihydrate is now known as Formoterol fumarate dihydrate

(synonym: formoterol fumarate = INN/USAN)

### DESCRIPTION

Formoterol fumarate dihydrate is ( $\pm$ )-2'-Hydroxy-5'-[(RS)-1-hydroxy-2-[(RS)-p-methoxy- $\alpha$ -methylphenethyl]-amino]ethyl] formanilide fumarate dihydrate. Formoterol fumarate dihydrate is a racemic mixture of two isomers with the configuration; R,R and S,S.

Formoterol fumarate dihydrate is a white to yellowish, odourless powder. It is freely soluble in glacial acetic acid; soluble in methanol; sparingly soluble in ethanol and isopropyl alcohol, slightly soluble in water; and practically insoluble in acetone, ethyl acetate and diethylether. The molecular formula is  $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ . The chemical structure of formoterol fumarate dihydrate (CAS Number: 43229-80-7) is as follows:



Foradile contains formoterol fumarate dihydrate 12 $\mu$ g with lactose as the excipient. The product is supplied in a size 3 gelatin capsule shell consisting of a clear body with a clear cap. The capsule shell is imprinted in black ink with "CG" on one part and "FXF" on the other.

Foradile capsules are for oral inhalation only. Foradile is also supplied with an AEROLIZER® inhalation device to permit oral inhalation of the contents of the capsule shell.

### PHARMACOLOGY

#### Pharmacodynamics

Formoterol belongs to a new class of potent, long-acting, selective  $\beta_2$ -adrenoceptor agonists.

It exerts a bronchodilator effect in patients with reversible airways obstruction.

The onset of bronchodilation occurs within 1 to 3 minutes and is still significant 12 hours after inhalation. The time to peak effect is 1 to 2 hours.

Formoterol inhibits the release of histamine and leukotrienes from passively sensitised human lung. Some anti-inflammatory properties, such as inhibition of oedema and inflammatory cell accumulation, have been observed in animal experiments.

In man, Foradile has been shown to be effective in preventing bronchospasm induced by inhaled allergens, exercise, cold air, histamine or methacholine. At therapeutic doses cardiovascular effects are minor and occur only occasionally.

### **Pharmacokinetics**

Formoterol acts locally in the lung, therefore, plasma levels are not predictive of therapeutic effect. Analysis of urinary excretion rates, suggests that inhaled formoterol is rapidly absorbed. The maximum excretion rate after administration of 12 to 96 µg is reached within 1 to 2 hours of inhalation in healthy young adults. At a higher than therapeutic dose (120 µg single dose), the peak plasma concentration (266 pmol/L) is observed at 5 minutes post inhalation. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 µg twice daily, the peak plasma concentrations occurred between 10 minutes and 2 hours after inhalation. On day 84, mean plasma concentrations were 7.6, 21.3, 25.7 and 11.5 pmol/L at 0, 10 minutes, 2 hours and 6 hours after inhalation in patients on 12 µg twice daily and 30.9, 43.2, 50.3 and 23.3 pmol/L at 0, 10 minutes, 2 hours and 6 hours in patients on 24 µg twice daily. Six to nine percent of an inhaled dose is excreted unchanged in the urine. Cumulative urinary excretion of formoterol after administration of the inhalation powder showed the amount of formoterol in the circulation to increase in proportion to dose.

The pharmacokinetics of formoterol fumarate dihydrate have been elucidated from oral administration of the drug. Administration of up to 300 µg orally of formoterol fumarate dihydrate showed that the drug is readily absorbed from the gastrointestinal tract. Peak plasma levels of unchanged drug are reached within 0.5 to 1 hour after administration. The absorption of an oral dose of 80 µg is 65% or more, although 70% of this dose undergoes pre-systemic or first pass metabolism. The pharmacokinetics of formoterol appear linear in the range of oral doses studied i.e. 20 to 300 µg. Repeated oral administration of 40 to 160 µg daily did not lead to significant accumulation of the drug.

Plasma protein binding of formoterol is 61 to 64% and no saturation of binding sites occurs with the concentration range reached with therapeutic doses. The major pathway for elimination is by direct glucuronidation and O-demethylation followed by glucuronidation, a minor pathway. The plasma concentration versus time profile of formoterol is polyphasic. On the basis of plasma or blood concentrations up to 6, 8 or 12 hours after oral administration, an elimination half-life of about 2 to 3 hours was determined. From urinary excretion rates between 3 and 16 hours after inhalation, a half-life of about 5 hours was calculated.

The drug and its metabolites are completely eliminated from the body; about two-thirds of an oral dose appear in the urine and one-third in the faeces. Renal clearance of formoterol from blood is 150 mL/min (2.2 mL/min/Kg).

**Special Populations:**Elderly patients:

The pharmacokinetics of formoterol have not been studied in the elderly population.

Hepatic impairment:

The pharmacokinetics of formoterol have not been studied in patients with hepatic impairment.

Renal impairment:

The pharmacokinetics of formoterol have not been studied in patients with renal impairment.

**CLINICAL TRIALS****Clinical Trials in Asthma**

Foradile Powder for Inhalation has been studied in several controlled multiple dose trials (in adults and children) and 3 open follow up studies (2 in adults and 1 in children). All controlled multiple dose studies began with a run-in or baseline period either one or two weeks, followed by a double blind treatment period of within-patient (cross-over) or between-patient (parallel group) design conducted with double dummies. Placebo and/or 400µg salbutamol (given four times a day or three times a day) were used as reference therapies. The studies included 258 asthmatic children (aged 5 - 15 years) and 1238 adults with reversible or partly reversible airways obstruction, 262 of which were elderly and aged 64 to 82 years.

Four of the controlled trials assessed the efficacy of Foradile given twice daily over a 12 week period. The following table lists the treatment differences of the primary efficacy parameter (predose morning PEFr) in these trials:

Protocol	No. of patients	Treatment difference	PEFR estimate	p value
DP/RD 1 (adults)	304 (18-71)	Foradile 12µg twice daily vs. placebo	26.9	<0.0001
		Foradile 12µg twice daily vs. salbutamol 400µg four times a day	32.1	<0.0001
		salbutamol 400µg four times a day vs. placebo	-5.2	0.323 (ns)
DP/RD 2 (adults)	318 (18-74)	Foradile 24µg twice daily vs. salbutamol 400µg four times a day	44.9	<0.0001
		Foradile 12µg twice daily vs. salbutamol 400µg four times a day	32.1	<0.0001
		Foradile 24µg twice daily vs. 12µg twice daily	12.8	0.053 (ns)
DP/RD3 (elderly)	262 (64-82)	Foradile 24µg twice daily vs. salbutamol 400µg four times a day	33.6	<0.0001
		Foradile 12µg twice daily vs. salbutamol 400µg four times a day	33.3	<0.0001
		Foradile 24µg twice daily vs. 12µg twice daily	0.3	0.96 (ns)
DP/PD2 (children)	219 (5-13)	Foradile 12µg twice daily vs. salbutamol 400µg three times a day	15.9	0.0008
		Foradile 6µg twice daily vs. salbutamol	4.5	0.3401 (ns)
		Foradile 12µg twice daily vs. 6µg twice daily	11.4	0.0133

These trials have shown that Foradile is a significantly better bronchodilator than salbutamol. In the adult studies, mean predose morning PEFr increased by approximately 40 - 50 L/min with Foradile. This increase was maintained for the duration of the studies. In two of the studies (DP/RD1 and DP/RD2) FEV<sub>1</sub> values did not increase significantly more with Foradile than with salbutamol but did in the third study (DP/RD3). Using the overall mean predose morning PEFr, although there was a trend in favour of 24 µg twice daily Foradile, this dose was not significantly more effective than 12µg twice daily in trial DP/RD2 and DP/RD3. The effect of Foradile in the elderly was found to be similar to younger adults. In study DP/PD2 (children), the morning PEFr improved significantly more with Foradile 12 µg twice daily than with salbutamol 400 µg three times a day. This dose of Foradile was also found to be more effective than Foradile 6 µg twice daily. Compared with regularly inhaled salbutamol, the use of Foradile resulted in significantly better predose evening PEFr, the need for significantly less rescue medication, significantly fewer day and night-time asthma symptoms, significantly less sleep disturbance and was judged to be better overall by patients and investigators.

375 adults and 69 children from the 3 month double blind studies completed a further 12 month open treatment period with Foradile. The doses of Foradile was 12-24 µg twice daily. The improvement in airways obstruction observed in the 3 month studies was maintained in adults and showed a tendency for further improvement in children over the 12 month follow-up period.

A crossover study in 78 adults with nocturnal asthma was also conducted (DP/NA1). Foradile 12 µg twice daily was compared with salbutamol 400 µg four times a day during 2

week treatment periods with no wash-out between. The night-time scores, morning tightness score, predose PEF, night rescue medication and overall assessment were significantly better with Foradile than salbutamol.

### **Clinical Trials in COPD**

Two large multinational, multicenter, randomized, double-blind, parallel group, controlled trials have been carried out in the target population of patients with COPD (protocols 056 and 058). Both were placebo-controlled and included an active comparator arm. The primary objective in both trials was to assess the efficacy of formoterol 12 µg and 24 µg twice daily by Aerolizer™ device compared with placebo. In both trials further analysis was made of patients classified as “reversible” or “irreversible” at baseline based on a cut-off of 15% increase in FEV1 30 minutes after inhalation of 200 µg salbutamol. Approximately 50% of patients had reversible COPD in both trials. Subjective measurement of “quality of life” (QoL) was made using the Saint George's Respiratory Questionnaire.

In protocol 056, both doses of formoterol produced statistically significant and clinically relevant bronchodilation compared to placebo over 3 months in a modified intention-to-treat analysis involving 194 patients receiving 12 µg twice daily, 192 that received 24 µg twice daily and 200 placebo. The mean increase in FEV1 in the 12 µg group was 224 mL, 95% confidence interval [174, 273], and, in the 24 µg group, 194 mL, 95% confidence interval [145, 243]. The mean increases were 241 mL and 213 mL for reversible and irreversible patients respectively at 12 µg, and 244 mL and 137 mL for reversible and irreversible patients respectively at 24 µg.

Formoterol treatment was associated with improved quality of life, lower use of rescue salbutamol and 10% fewer ‘bad days’ compared to placebo, ‘bad days’ being days with scores > 2 (out of 3) on 2 or more symptoms or > 20% reduction in peak expiratory flow rate. Bronchodilation was maintained over the 12 hour dosing interval.

There were no significant differences between the two doses of formoterol, nor were there clinically relevant differences between inhaled ipratropium bromide 40 µg four times a day and formoterol.

Similar results were obtained in protocol 058, which involved 191 patients who received formoterol 12 µg twice daily, 197 that received 24 µg twice daily and 186 placebo for 12 months. The mean increase in FEV1 at 3 months in the 12 µg group was 200 mL, 95% confidence interval [144, 257], and, in the 24 µg group, 208 mL, 95% confidence interval [152, 264]. The mean increases were 331 mL and 109 mL for reversible and irreversible patients respectively at 12 µg, and 271 mL and 166 mL for reversible and irreversible patients respectively at 24 µg. The increases were sustained at 12 months, being 207 mL, 95% confidence interval [143, 272], in the 12 µg group and 170 mL, 95% confidence interval [107, 233], in the 24 µg group. There were no clinically relevant differences between sustained-release theophylline tablets 200-400 mg twice daily and formoterol.

## **INDICATIONS**

Foradile is indicated for the long-term, regular treatment of reversible airways obstruction in asthma (including nocturnal asthma and exercise-induced asthma) in patients aged 5 years or more who are receiving inhaled or oral corticosteroids. It should not be used in patients whose asthma can be managed by occasional use of short-acting inhaled beta-2 agonists.

Foradile is also indicated for the prophylaxis and treatment of bronchoconstriction in patients with reversible or irreversible chronic obstructive pulmonary disease (COPD).

## **CONTRAINDICATIONS**

Hypersensitivity to any ingredients of the preparation.

Foradile capsules contain lactose. Therefore, patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **PRECAUTIONS**

### **General**

Foradile should not be initiated in patients with unstable or acutely deteriorating asthma. The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

### **Anti-Inflammatory Therapy**

Foradile should not be used in conjunction with another long-acting  $\beta$ -2 adrenoceptor agonist.

Foradile is not a substitute for anti-inflammatory therapy. When treating patients with asthma, use Foradile, a long-acting beta2-agonist (LABA) only as additional therapy for patients not adequately controlled on an inhaled corticosteroid (ICS) alone or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA.

In patients not currently receiving anti-inflammatory therapy, this must be initiated at the same time as Foradile. Whenever Foradile is prescribed, patients should be evaluated for the adequacy of the anti-inflammatory therapy they receive. Patients must be advised to continue taking their anti-inflammatory therapy unchanged after the introduction of Foradile, even when their symptoms improve. Should symptoms persist, or should the number of doses of rescue medication required to control symptoms increase, this usually indicates a worsening of the underlying condition and warrants a reassessment of asthma therapy by the physician.

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

### **Acute Asthma**

Foradile should not be used for the management of acute episodes or exacerbation of asthma. Although Foradile has a rapid onset of action, current asthma management guidelines recommend that long-acting inhaled bronchodilators should be used as maintenance bronchodilator therapy. They further recommend that in the event of an acute attack, a  $\beta_2$ -adrenoceptor agonist with a short duration of action should be used. Patients should be advised to have such rescue medication available. Effective drug delivery through dry powder inhalation devices is dependent on inspiratory airflow. Some younger children (i.e. 5 years or younger) may not be able to use such devices effectively. This difficulty may be aggravated in acute attacks.

### **Asthma Exacerbations**

Clinical studies with Foradile suggested a higher incidence of serious asthma exacerbations in patients who received Foradile than those who received placebo (see “ADVERSE EFFECTS”). These studies do not allow precise quantification of the differences in serious asthma exacerbation rates between research groups.

### **Deterioration**

Increasing use of bronchodilators indicates deterioration of asthma control. If patients find that relief from short acting bronchodilators becomes less effective or they need more inhalations than usual, medical attention must be sought. In this situation, patients should be reassessed and consideration be given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroids). Patients should be advised to have such medication available. Severe exacerbations of asthma must be treated in the normal way with nebulised or parenteral bronchodilators and parenteral corticosteroids, together with supportive measures.

### **Paradoxical Bronchospasm**

As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If this occurs, Foradile should be discontinued and alternative therapy substituted.

### **Incorrect route of administration**

There have been reports of patients who have mistakenly swallowed Foradile capsules instead of placing the capsules in the AEROLIZER<sup>®</sup> inhalation device. The majority of these ingestions were not associated with side effects. Healthcare providers should discuss with the patient how to correctly use Foradile AEROLIZER<sup>®</sup> (see ‘DOSAGE AND ADMINISTRATION’). If a patient who is prescribed Foradile AEROLIZER<sup>®</sup> does not experience breathing improvement, the healthcare provider should ask how the patient is using Foradile AEROLIZER<sup>®</sup>.

### **Concomitant Conditions**

Special care and supervision, with particular emphasis on dosage limits, is required in patients receiving Foradile who have the following conditions:

- Ischaemic heart disease, cardiac arrhythmias; especially third degree atrioventricular block, severe cardiac decompensation, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm, phaeochromocytoma, hypertrophic obstructive cardiomyopathy, known or suspected prolongation of the QT interval [QTc>0.44 sec.; (see "INTERACTIONS WITH OTHER MEDICINES")].
- Thyrotoxicosis.

Due to the hyperglycaemic effect of  $\beta_2$ -adrenoceptor agonists, including Foradile, additional blood glucose controls are recommended in diabetic patients.

### **Hypokalaemia**

Potentially serious hypokalaemia may result from  $\beta_2$ -adrenoceptor agonist therapy, including Foradile. Particular caution is advised in severe asthma as this effect may be potentiated by hypoxia and concomitant medications (see "INTERACTIONS WITH OTHER MEDICINES"). Hypokalaemia may increase susceptibility to cardiac arrhythmias. It is recommended that serum potassium levels be monitored in such situations.

### **Asthma Related Deaths**

Formoterol, the active ingredient of Foradile, belongs to the class of long-acting  $\beta_2$ -adrenoceptor agonists. In a study with salmeterol, a different long-acting  $\beta_2$ -agonist, a higher rate of death due to asthma was observed in the patients treated with salmeterol (13/13176) than in the placebo group (3/13179). No study adequate to determine whether the rate of asthma related death is increased with Foradile has been conducted.

### **Mutagenicity and Carcinogenicity**

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.

In carcinogenicity studies, addition of formoterol fumarate to the drinking water caused adrenal subcapsular cell tumours in male mice dosed at 66 - 225 mg/kg/day, thyroid C-cell neoplasms in male rats dosed at 46 mg/kg/day, mesovarian leiomyomas in female rats dosed at 18 - 72 mg/kg/day, and an increased incidence of mammary adenocarcinoma in female rats dosed at 36 or 72 mg/kg/day. The results of these studies must be treated with caution in view of the excessive dose levels used, which resulted in systemic exposure levels 200 - 1200 fold higher than those expected upon clinical use of formoterol fumarate (based on a 72  $\mu\text{g}$  daily dose). As a consequence of this the studies were repeated. In the repeated studies drug was administered with the feed. Hepatocellular adenomas and carcinomas were observed in male and female mice at dose levels greater than 2 mg/kg/day; leiomyomas and



leiomyosarcomas were seen in the reproductive tract of female mice dosed at 2 - 50 mg/kg/day. Mesovarian leiomyomas were observed in rats dosed at 2 - 20 mg/kg/day and benign granulosa/theca cells in the ovaries of rats dosed at 0.5 - 20 mg/kg/day. Plasma drug concentrations at dose levels associated with these carcinogenic effects, based on AUC values, were estimated to be at least ten times higher than the maximum systemic exposure anticipated in humans.

Mammary adenocarcinomas and smooth muscle tumours in the female reproductive system and effects on the ovary have been reported in rats or mice treated with other beta<sub>2</sub>-adrenoceptor agonists, and are likely to be secondary to prolonged stimulation of beta<sub>2</sub>-adrenoceptors in these tissues. Thyroid C-cell tumours were only seen at doses resulting in systemic exposure several hundred fold higher than that expected at the highest recommended human dose. They are thought to be a consequence of stimulation of calcitonin secretion as a result of bone growth, secondary to beta-agonist induced anabolic effects on skeletal muscle at excessive formoterol fumarate doses. The mechanism underlying the induction of hepatocellular tumours and adrenal subcapsular tumours in the mouse is unclear. However, in view of the dose levels at which these effects were observed and the fact that formoterol fumarate is not mutagenic, it is concluded that the cancer risk in patients treated with formoterol fumarate is no greater than for other β-adrenoceptor agonists.

Long-term treatment of female mice and rats with formoterol fumarate causes ovarian stimulation, the development of ovarian cysts and hyperplasia of granulosa/theca cells as a result of the beta-agonist properties of the compound. No effect was seen on fertility of female rats dosed orally with formoterol fumarate at 60 mg/kg/day for two weeks. Testicular atrophy was observed in mice given formoterol fumarate in the diet at 0.2 - 50 mg/kg/day for two years, but no effect on male fertility was observed in rats dosed orally at 60 mg/kg/day for nine weeks.

### **Use in Pregnancy (Pregnancy Categorisation B3)**

No teratogenic effects were observed in rats receiving formoterol fumarate at oral doses of up to 60 mg/kg/day or in rabbits given formoterol fumarate at oral doses of up to 500 mg/kg/day over the period of organogenesis. Decreased birth weight and increased perinatal mortality were observed when formoterol fumarate was given to rats at oral doses greater than 3 mg/kg/day during late gestation.

The safety of Foradile during pregnancy has not yet been established. Until further experience has been acquired, use in pregnancy should be avoided unless there is no safer alternative. Beta<sub>2</sub>-adrenoceptor agonists including formoterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

### **Use in Lactation**

It is not known whether formoterol passes into human breast milk. Formoterol fumarate and/or its metabolites was excreted in the breast milk of lactating rats given oral doses of 50µg/kg of drug, and growth and survival of the pups were decreased when lactating rats

were given formoterol fumarate at oral doses greater than 1 mg/kg/day. Women who are breastfeeding should not use Foradile unless in the opinion of the physician the benefits of therapy outweigh the risks.

### **Paediatric Use**

Foradile is not recommended in children under 5 years. For the dosage in children 5 years and over (see "DOSAGE AND ADMINISTRATION").

### **Effects on Ability to Drive and Use Machines**

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

## **INTERACTIONS WITH OTHER MEDICINES**

The undesirable cardiovascular effects of Foradile may be potentiated by its concomitant administration with a number of drugs. This should be kept in mind when treating patients on monoamine oxidase inhibitors or tricyclic antidepressants as well as those on quinidine, disopyramide, procainamide, phenothiazines or antihistamines, macrolides or any drugs known to be associated with QTc-interval prolongation and an increased risk of ventricular arrhythmia (see "PRECAUTIONS - Concomitant conditions").

Concomitant administration of other sympathomimetic amines may also potentiate the undesirable effects of Foradile.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of  $\beta_2$ -adrenoceptor agonists. Hypokalaemia may increase susceptibility to cardiac arrhythmias.

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

Beta-adrenoceptor blockers may weaken or antagonise the effect of Foradile. Therefore, Foradile should not be given together with  $\beta_2$ -adrenoceptor blockers (including eye drops) unless there are compelling reasons for their use.

## **ADVERSE EFFECTS**

### **Serious Asthma Exacerbations**

Placebo-controlled clinical studies of at least 4 weeks treatment duration with Foradile suggested a higher incidence of serious asthma exacerbations in patients who received Foradile (0.9% for 10-12 $\mu$ g twice daily, 1.9% for 24 $\mu$ g twice daily) than in those who received placebo (0.3%).

### **Experience in Adolescent and Adult Patients with Asthma**

In two pivotal 12-week controlled trials conducted for US registration with combined enrolment of 1095 patients 12 years of age and older, serious asthma exacerbations (acute worsening of asthma resulting in hospitalisation) occurred more commonly with Foradile 24µg twice daily (9/271, 3.3%) than with Foradile 12 µg twice daily (1/275, 0.4%), placebo (2/277, 0.7%) or salbutamol (2/272, 0.7%).

A subsequent clinical trial to address this observation enrolled 2085 patients to compare asthma-related serious adverse events in the higher and lower dose groups. The results from this 16 week trial did not show an apparent dose-relationship for Foradile. The percent of patients with serious asthma exacerbations in this study was somewhat higher for Foradile than for placebo (for the three double-blind treatment groups: Foradile 24µg twice daily (2/527, 0.4%), Foradile 12µg twice daily (3/527, 0.6%), and placebo (1/514, 0.2%) and for the open-label treatment group: Foradile 12 µg twice daily plus up to two additional doses per day (1/517, 0.2%).

### **Experience in Children aged 5-12 years with Asthma**

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

### **Other Adverse Effects**

Adverse reactions are defined according to frequency as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100 < 1/10$ ); uncommon ( $\geq 1/1000, < 1/100$ ); rare ( $\geq 1/10,000 < 1/1,000$ ); very rare ( $< 1/10,000$ ), including isolated reports.

Musculoskeletal system:

Common: tremor  
 Uncommon: muscle cramps, myalgia

Cardiac disorders:

Common: palpitations  
 Uncommon: tachycardia,  
 Very rare: Peripheral oedema

Psychiatric disorders:

Uncommon: agitation, anxiety, nervousness, insomnia

Central nervous system disorders:

Common: headache, dizziness, tremor  
 Uncommon: fatigue, insomnia, dizziness  
 Very rare: dysgeusia

Respiratory tract, thoracic and mediastinal disorders:

Common: cough, pharyngitis, dysphonia, dyspnoea  
 Uncommon: chest pain, increased sputum, bronchospasm, including paradoxical bronchospasm

Local irritation:

Common: throat irritation, dry mouth

Immune system disorders

Very rare: hypersensitivity reactions including hypotension, urticaria, angioneurotic oedema, oedema (including conjunctival irritation and eyelid oedema), pruritus, exanthem

Gastrointestinal disorders

Very rare: nausea

**Post-Marketing**

The following post-marketing events have been reported in patients treated with Foradile. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

<u>Metabolism and nutrition disorders:</u>	hypokalaemia, hyperglycaemia
<u>Investigations:</u>	electrocardiogram QT prolonged, blood pressure increased (including hypertension)
<u>Skin and subcutaneous tissue disorders:</u>	rash
<u>Cardiac disorders:</u>	Angina pectoris, cardiac arrhythmias e.g. atrial fibrillation, ventricular extrasystoles, tachyarrhythmia
<u>Respiratory, thoracic and mediastinal disorders:</u>	Cough

**DOSAGE AND ADMINISTRATION**

The dose of Foradile should be individualised to the patients needs and should be at the lowest possible dose to fulfil the therapeutic objective. It should not be increased beyond the maximum recommended dose.

**Adults**

**Asthma:** 1 to 2 capsules (12 to 24 µg), to be inhaled twice daily. The total daily dose should not exceed 48 µg.

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

**COPD:** 1 capsule (12 µg) to be inhaled twice daily

**Children Aged 5 years and Over**

1 capsule (12 µg) to be inhaled twice daily, Foradile should only be prescribed as an add-on to an inhaled corticosteroid. The total daily dose should not exceed 24 µg.

**Patients 65 years and Over**

No dosage adjustment from the adult dose is required in this patient population.

**Instructions for Use**

The capsules should only be removed from the blister pack and placed in the device immediately before use. Failure to observe this instruction may result in insufficient medication being released by the device due to possible unfavourable storage of the capsules.

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 this to happen is minimised by not piercing the capsule more than once.

The patient should also be instructed to check that they have inhaled the entire content of the capsule shell before discarding the shell.

**OVERDOSAGE**

An overdose of Foradile is likely to lead to effects that are typical of  $\beta$ -adrenoceptor stimulants: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia, hypertension.

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  $\beta$ -adrenoceptor blocker medication may provoke bronchospasm.

Contact *Poisons Information Centre* on 131126 for advice on management of overdose.

**PRESENTATION AND STORAGE CONDITIONS**

Foradile (formoterol fumarate dihydrate) Capsules 12  $\mu$ g are supplied in blister packs of 30 and 60 with an AEROLIZER<sup>®</sup> inhalation device to allow oral inhalation of the content of the capsule shell.

**NAME AND ADDRESS OF THE SPONSOR**

NOVARTIS Pharmaceuticals Australia Pty. Limited  
ABN 18 004 244 160  
54 Waterloo Road  
Macquarie Park NSW 2113

® = Registered Trademark

**POISON SCHEDULE OF THE MEDICINE**

Schedule 4

**DATE OF FIRST INCLUSION IN THE ARTG**

29 January 1997

**DATE OF MOST RECENT AMENDMENT**

Date of most recent amendment: 25 November 2016

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