PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}FORADIL®

Formoterol fumarate Dry Powder Capsules for Inhalation

12 mcg formoterol fumarate per capsule

Capsules to be used only with the supplied Aerolizer® inhalation device

Bronchodilator

(beta$_2$-adrenergic stimulant)

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RECENT MAJOR LABEL CHANGES

None at the time of authorization

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ASTHMA:

FORADIL® (formoterol fumarate) is indicated for the treatment of asthma only as add-on therapy to inhaled corticosteroid; a long-term asthma control medication; in patients 6 year of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.

Corticosteroids should not be stopped because formoterol is prescribed.

Long-acting beta2-adrenergic agonists (LABA), such as formoterol, the active ingredient in FORADIL, increase the risk of asthma-related death (see 7 WARNINGS AND PRECAUTIONS). Use of FORADIL for the treatment of asthma without concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated (see 2 CONTRAINDICATIONS). Use FORADIL only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Formoterol is a long-acting beta2-agonist and should not be used as a rescue medication. To relieve acute asthmatic symptoms a short-acting inhaled bronchodilator (e.g. salbutamol) should be used.

Pediatric and Adolescent Patients

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see 7 WARNINGS AND PRECAUTIONS). For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate inhaled corticosteroid and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD):

FORADIL (formoterol fumarate) is indicated as long-term, twice-daily administration in the treatment of adults with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

1.1 Pediatrics

Pediatrics (< 6 years of age): FORADIL is not recommended for use in children younger than 6 years of age.

1.2 Geriatrics

Geriatrics (> *65* years of age): No special considerations are required in elderly patients.

2 CONTRAINDICATIONS

Because of the risk of asthma-related death and hospitalization, use of FORADIL for the treatment of asthma without concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated (see 7 WARNINGS AND PRECAUTIONS).

FORADIL (formoterol fumarate) is contraindicated in patients with cardiac tachyarrhythmias. FORADIL contains lactose (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING) and is contraindicated in patients with an allergy to lactose, milk or in those who have ever had any unusual or allergic reaction to formoterol fumarate.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Use in Asthma **Serious Warnings and Precautions**

WARNING: ASTHMA RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL, increase the risk of asthma-related death. Data from a large placebo controlled US study that compared the safety of another LABA (salmeterol) or placebo added to patients usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of FORADIL for the treatment of asthma without a concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated (see 2 CONTRAINDICATIONS). Use FORADIL only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids (see 4 DOSAGE AND ADMINISTRATION).

Pediatric and Adolescent Patients

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate inhaled corticosteroid and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components.

If adherence cannot be assured, a fixed-dose combination product containing both an inhaled

corticosteroid and LABA is recommended (see 4 DOSAGE AND ADMINISTRATION).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General considerations for Asthma and COPD

Foradil should not be used more than twice daily with a twelve-hour interval between doses.

FORADIL should not be used to treat acute symptoms. It is crucial to inform patients of this and prescribe a short-acting, inhaled beta$_2$-agonist for this purpose. The need for additional symptomatic bronchodilator therapy is usually reduced with FORADIL. Medical attention should be sought if patients find that short-acting relief bronchodilator treatment becomes less effective or if they need more inhalations than usual. This is a sign of seriously worsening asthma that requires reassessment of therapy.

Renal impairment

Formoterol has not been studied in patients with renal impairment (see 10 CLINICAL PHARMACOLOGY).

Hepatic impairment

Formoterol has not been studied in patients with hepatic impairment (see 10 CLINICAL PHARMACOLOGY).

Geriatrics (older than 65 years)

The pharmacokinetics of formoterol has not been studied in the elderly population (See 10 CLINICAL PHARMACOLOGY). There is no information suggesting that the dosage in geriatric patients should be different than in other adults (see 14 CLINCIAL TRIALS)

Asthma:
Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, the active ingredient in FORADIL, increase the risk of asthma-related death (see 7 WARNINGS AND PRECAUTIONS). **Because of this risk, use of FORADIL for the treatment of asthma without concomitant use of an inhaled corticosteroid; a long-term asthma control medication; is contraindicated** (see 2 CONTRAINDICATIONS). Use FORADIL only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids (see 7 WARNINGS AND PRECAUTIONS).

FORADIL (formoterol fumarate) should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition (see 7 WARNINGS AND PRECAUTIONS).

FORADIL is not a replacement for inhaled or oral corticosteroid therapy; its use is complementary to it. Patients must be warned not to stop or reduce anti-inflammatory therapy (see 2 CONTRAINDICATIONS).

Bronchodilators should not be the only or main treatment in patients with moderate to severe asthma. Patients with severe asthma require regular medical assessment since death may occur. These patients will require high-dose inhaled or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroids dosage which should be administered under medical supervision (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

Asthma:

Adults: One capsule (12 mcg of formoterol fumarate) is inhaled using the Aerolizer inhaler twice daily, in the morning and evening. In severe cases, adults may require two capsules (2 X 12 mcg) twice daily, in the morning and evening. In adults, the maximum recommended daily dose of FORADIL is 48 mcg.

FORADIL should not be used to relieve the acute symptoms of an asthma attack. In the event of an acute attack, a short-acting beta$_2$-agonist should be used (see 7 WARNINGS AND PRECAUTIONS). FORADIL should only be prescribed as an add-on to an inhaled corticosteroid.

Children (6 - 16 years) : One capsule (12 mcg of formoterol fumarate) is inhaled using the Aerolizer inhaler twice daily, in the morning and evening. The maximum recommended dose is 24 micrograms per day. FORADIL should only be prescribed as an add-on to an inhaled corticosteroid.

COPD:

Adults: One or two capsules (12 mcg or 24 mcg of formoterol fumarate) is inhaled using the Aerolizer inhaler twice daily, in the morning and evening**.**

4.4 Administration

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 7 WARNINGS AND PRECAUTIONS)

Detailed handling instructions are included in the package leaflet.

Only use FORADIL capsules with the Aerolizer inhaler that is provided with each prescription refill. Do not use another type of inhaler with the capsules. Do not use other capsules in the Aerolizer inhaler.

Always use the new Aerolizer inhaler that is supplied with each prescription refill. To ensure proper administration of the drug, the physician or other health professional should show the patient how to operate the Aerolizer inhaler.

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 during inhalation. The tendency for this to happen is minimized by not piercing the capsule more than once.

Remove the capsules from the blister pack **only immediately** before use.

The emitted dose from one capsule when inhaled by the Aerolizer inhaler is 9.6 mcg.

4.5 Missed Dose

FORADIL should not be used more often than twice a day. Patients should be advised that if they forget to take a dose, they should take it as soon as they remember. However, if it is almost time for the next dose, the patient should not take the missed one and just go back to the regular dosing schedule. The patient should never take a double dose.

5 OVERDOSAGE

Symptoms

An overdosage of FORADIL (formoterol fumarate) is likely to lead to effects that are typical of $beta_2$-adrenergic stimulants: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalemia, hyperglycemia, hypertension.

Treatment

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

Use of cardioselective beta-adrenergic blockers may be considered, but only under the supervision of a physician subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Inhalation	12 mcg formoterol fumarate dry powder capsules	gelatin, lactose monohydrate, shellac glaze 45%, black iron oxide, Isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, dehydrated ethanol, ammonium hydroxide 28%

FORADIL (formoterol fumarate) 12 mcg capsules

Each clear hard gelatin capsule of white free flowing powder for inhalation only, contains formoterol fumarate (12 mcg).

Use capsules only with the supplied Aerolizer inhalation device. One Aerolizer inhalation device and 60 capsules are supplied with each carton.

Each 12 mcg capsule of FORADIL contains lactose monohydrate (25 mg/capsule) and gelatin.

7 WARNINGS AND PRECAUTIONS

General

FORADIL (formoterol fumarate) should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition.

FORADIL is intended for the maintenance treatment of asthma (see Indications and Clinical Use) and should not be introduced in acutely deteriorating asthma, which is a potentially life threatening condition. There are no data demonstrating that long-acting beta$_2$-agonists provide greater efficacy than or additional efficacy to short-acting, inhaled beta$_2$-agonists in patients with worsening asthma. As with other long-acting beta$_2$-agonists, serious acute respiratory events, including fatalities, have been reported in patients receiving FORADIL, some of which have occurred in patients with severe asthma and/or patients in whom asthma has been acutely deteriorating. Although it is not possible from these reports to determine the causal relationship between long-acting beta$_2$-agonists and these adverse events, the use of a long-acting beta$_2$-agonist in patients with acutely deteriorating asthma is inappropriate.

For children 6-12 years of age, treatment with a combination product containing an inhaled corticosteroid and long-acting beta$_2$-agonist is recommended, except in case where a separate inhaled corticosteroid and long-acting beta$_2$-agonist are required (see 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS).

FORADIL should not be used in conjunction with another long-acting beta$_2$-agonist.

Asthma exacerbations

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 6-12 years of age. These studies do not allow precise quantification of the differences in serious asthma exacerbation rates between treatment groups.

The physician should reassess asthma therapy if symptoms persist, or if the number of doses of FORADIL required to control symptoms increases, because this usually indicates that the underlying condition has deteriorated.

FORADIL must not be initiated or the dose increased during an asthma exacerbation.

FORADIL should not be used to treat acute symptoms. It is crucial to advise patients accordingly and prescribe a short-acting, inhaled bronchodilator for this purpose. Medical attention should be sought if patients find that short-acting relief bronchodilator treatment becomes less effective or that they need more inhalations than usual.

When beginning treatment with FORADIL, patients who have been taking short-acting, inhaled beta$_2$-agonists on a regular basis (e.g., q.i.d.) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute asthma symptoms while using FORADIL. Although formoterol has a rapid onset of action (1 to 3 min.), current asthma management guidelines recommend that long-acting inhaled bronchodilators should be used only as twice-daily maintenance bronchodilator therapy.

Asthma management

The management of asthma should normally follow a stepwise program, with patient response closely monitored and lung function tests regularly conducted. The following recommendations are stated in the current Canadian Consensus Guidelines for the long-acting beta$_2$-adrenergic agonists:

- Oral or inhaled corticosteroids should not be stopped.
- Long-acting beta$_2$-adrenergic agonists should not be used as monotherapy.
- Long-acting beta$_2$-adrenergic agonists should be used as add-on therapy to inhaled corticosteroids.
- Adequate education should be provided to the patient regarding the use of long-acting beta$_2$-agonists and the acute treatment of asthma, with close follow-up to ensure compliance.
- Long-acting beta$_2$-agonists should not be introduced in patients with significantly worsening or acutely deteriorating asthma.

Increasing use of short-acting inhaled beta$_2$-agonists to control symptoms indicates deterioration of asthma control and the need to reassess the patient's therapy.

Sudden or progressive deterioration in asthma control is potentially life-threatening; the treatment plan must be re-evaluated, and consideration given to increasing corticosteroid therapy. In patients at risk, daily peak flow monitoring with precise instructions for acceptable variation limits should be considered.

Beta-Adrenergic Blockers

Beta-adrenergic blockers, especially noncardioselective agents, should not be administered to asthmatic patients (see 9 DRUG INTERACTIONS) since these antagonize the action of beta$_2$-agonists including FORADIL and may produce severe, resistant bronchospasm.

DO NOT EXCEED RECOMMENDED DOSAGE

Fatalities, the exact cause of which is unknown, have been reported following excessive use of inhaler preparations containing sympathomimetic amines. The exact cause of death is unknown but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. In individual patients, any beta$_2$-agonist may have a clinically adverse cardiac effect. The incidence of mortality in patients receiving FORADIL is consistent with that typically seen in the asthmatic population. In an open-label, uncontrolled study conducted in Europe an overall crude mortality rate of approximately 14 per 1000 person years (8 of 1393 patients followed for 4.8 ± 2.6 months) was reported.

Cardiovascular

Usually no effect on the cardiovascular or central nervous system is seen after the administration of formoterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased heart rate, cardiac contractility, tremor) can occur while using formoterol. Potentially serious ECG changes and hypokalemia were seen at increased doses (96 mcg or 4 times the recommended maximum dose) of inhaled formoterol (See 14 CLINICAL TRIALS, Study Results).

It is not known if these effects become clinically significant when concomitant medications causing similar effects are prescribed and/or in the presence of heart diseases, hypokalemia, or hypoxia.

Particular caution is advised in severe asthma as these effects may be potentiated by hypoxia and concomitant treatment with xanthine derivatives, steroids and diuretics.

Therefore, special care and supervision, with particular emphasis on dosage limits, is required in patients receiving FORADIL when the following conditions may exist: ischemic heart disease, cardiac arrhythmias, especially third degree atrioventricular block, severe cardiac decompensation, idiopathic subvalvular aortic stenosis, hypertension, aneurysm, phaeochromocytoma, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, known or suspected prolongation of the QT-interval (QTc > 0.44 sec). Formoterol itself may induce prolongation of the QTc interval.

Use with caution in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

Do not exceed recommended dosage

As with other inhaled beta$_2$-agonist drugs, FORADIL should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs (see below).

Do not use in conjunction with an inhaled long-acting beta$_2$-agonist

FORADIL should not be used with other medications containing long-acting beta$_2$-agonists

Driving and Operating Machinery

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

Endocrine and Metabolism

Hypokalemia

Potentially serious hypokalemia may occur as a result of beta$_2$-agonist therapy, including FORADIL. Hypokalemia may increase susceptibility to cardiac arrhythmias. Particular caution is advised in patients with severe asthma as hypokalemia may be potentiated by hypoxia and concomitant treatment. It is recommended that serum potassium levels be monitored in such situations.

Immune

Immediate hypersensitivity reactions

Immediate hypersensitivity reactions may occur after administration of FORADIL. FORADIL contains lactose and is contraindicated in patients with allergy to lactose, milk or in those who have ever had any unusual or allergic reaction to formoterol fumarate (see 2 CONTRAINDICATIONS).

Incorrect route of administration

There have been reports of patients who have mistakenly swallowed FORADIL capsules instead of placing the capsules in the Aerolizer inhalation device. The majority of these ingestions were not associated with side effects. Health professionals should discuss with the patient how to correctly use FORADIL Aerolizer (See 4 DOSAGE AND ADMINISTRATION). If a patient who is prescribed FORADIL Aerolizer does not experience breathing improvement, the health professional should ask how the patient is using FORADIL Aerolizer

Increased need for short-acting, inhaled beta$_2$-agonists:

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's short-acting inhaled beta$_2$-agonist becomes less effective or a patient needs more inhalation than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires reassessment of the treatment regimen. Those patients who require increasing doses or inhalations of short-acting beta$_2$-agonists for relief of symptoms should consult a physician for re-evaluation. **Increasing the daily dosage of FORADIL in this situation is not appropriate. FORADIL should not be used more frequently than twice daily or at higher doses than recommended.**

FORADIL is not a substitute for inhaled or oral corticosteroids. Its use is complementary to them. Corticosteroids should not be stopped when FORADIL is initiated. Patients must be warned not to stop or reduce corticosteroid therapy (see 2 CONTRAINDICATIONS).

Metabolic effects

Due to the hyperglycemic effect of beta$_2$-stimulants including FORADIL, additional blood glucose controls are recommended in diabetic patients.

Respiratory

Paradoxical Bronchospasm

As with other inhaled medication, paradoxical bronchospasm (which can be life threatening) has been reported following the use of FORADIL. If it occurs, treatment with FORADIL should be discontinued immediately and alternative therapy instituted.

Reproductive Health: Female and Male Potential

- **Fertility :** There is no available data on the effect of formoterol on human fertility.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of FORADIL during pregnancy has not yet been established (see 7 WARNINGS AND PRECAUTIONS, Breast-feeding, Use in Labour and Delivery). Its use during pregnancy should be avoided unless there is no safer alternative.

Use in labour and delivery

There are no well-controlled human studies that have investigated the effects of formoterol on preterm labour or labour at term. Because of the potential for beta-agonist interference with uterine contractibility, use of beta$_2$-agonists, such as FORADIL, during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

7.1.2 Breast-feeding

FORADIL was found to be excreted in the milk of lactating rats after oral administration. It is not known whether inhaled FORADIL passes into the breast milk in humans. Therefore, mothers nursing their infants should refrain from taking FORADIL.

7.1.3 Pediatrics

Pediatrics (*< 6* years of age): FORADIL is not recommended for use in children younger than 6 years of age.

Pediatrics (6-12 years of age): In children 6-12 years of age the severity of asthma may be variable with age and periodic reassessment should be considered to determine if continued maintenance therapy with FORADIL is still indicated. Compliance, especially neglect of anti-inflammatory therapy and overuse of short-acting beta$_2$-agonists, should be carefully followed in children 6-12 years of age receiving long-acting beta$_2$-agonists.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate inhaled corticosteroid and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

7.1.4 Geriatrics

No special considerations are required in elderly patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse reactions observed with FORADIL (formoterol fumarate) in controlled, comparative and non-comparative clinical studies were dose-dependent and corresponded to those known to occur with other beta$_2$-adrenergic agonists.

Long-acting beta$_2$-adrenergic agonists (LABA), including formoterol, the active ingredient in FORADIL, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. Clinical trials with FORADIL suggested a higher incidence of serious asthma exacerbations in patients who received FORADIL than in those who received placebo (See 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Asthma:

The most common adverse reactions (< 10%) were tremor, palpitations, headache, dizziness and oropharyngeal irritation. Rarely (<1.0%) muscle cramps, myalgia, tachycardia, agitation, anxiety, nervousness, insomnia, and, very rarely (<0.01%) aggravated bronchospasm was reported.

The clinical trial program conducted with FORADIL has involved over 6000 patients. The profile of adverse events considered to be causally related to treatment from three controlled multidose trials of 3 months duration with FORADIL dry powder inhaler is presented in the following table.

Table 2 - Adverse event profile in three 3 -month controlled trials (≥ 1%)					
	Total number of patients reporting (%)				
	Formoterol			**Salbutamol**	**Placebo**
	I: 12 mcg b.i.d.	II: 24 mcg b.i.d.	I+II	400 mcg q.i.d.	
Total number of patients	292	197	489	294	101
Cardiovascular system					
Palpitation	2 (0.7)	5 (2.5)	7 (1.4)	10 (3.4)	1 (1.0)
Nervous system					
Tremor	6 (2.1)	10 (5.1)	16 (3.3)	6 (2.0)	1 (1.0)
Headache	9 (3.1)	4 (2.0)	13 (2.7)	10 (3.4)	2 (2.0)
Dizziness	5 (1.7)	2 (1.0)	7 (1.4)	3 (1.0)	0

The adverse event profile in three controlled clinical trials of up to 12 months duration in children 5-15 years of age was similar to that reported in adults.

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 (0.9% for 10 to12 micrograms twice daily, 1.9% for 24 micrograms twice daily) than in those who received placebo (0.3%), particularly in patients 6-12 years of age.

Experience in adolescent and adult patients with asthma

In two pivotal 12-week controlled trials conducted for US registration with combined enrollment of 1,095 patients 12 years of age and older, serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with FORADIL 24 micrograms twice daily (9/271, 3.3%) than with FORADIL 12 micrograms twice daily (1/275, 0.4%), placebo (2/277, 0.7%), or albuterol (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 FORADIL. The percent of patients with serious asthma exacerbations in this study was somewhat higher for FORADIL than for placebo (for the three double-blind treatment groups: FORADIL 24 micrograms twice daily (2/527, 0.4%), FORADIL 12 micrograms twice daily (3/527, 0.6%), and placebo (1/514, 0.2%) and for the open-label treatment group: FORADIL 12 micrograms twice daily plus up to two additional doses per day (1/517, 0.2%).

COPD:

FORADIL has been evaluated for safety in patients with COPD in two multi-centre, controlled studies with ipratropium or theophylline as reference therapy. In these studies, the maximum exposure to ipratropium was 3 months compared with 12 months for the other groups (formoterol, placebo and theophylline).

The type and most frequent adverse events that were considered treatment-related and occurred at an incidence of ≥ 1% in the FORADIL treated groups are presented in table 3.

Table 3 - Most frequent adverse events considered treatment-related and occurred at an incidence of ≥ 1%

	Total number of patients reporting (%)					
	Formoterol			**Placebo**	**Ipratropium**	**Theophylline**
	I: 12 mcg b.i.d.	II: 24 mcg b.i.d.	I + II		40 mcg q.i.d.	200 - 400* mg b.i.d.
Total number of patients	405	406	811	420	194	209
Digestive System						
Dry mouth	4 (1.0)	3 (0.7)	7 (0.86)	2 (0.48)	2 (1.0)	0
Musculoskeletal System						
Cramps muscle	4 (1.0)	9 (2.2)	13 (1.6)	0	2 (1.0)	0
Nervous System						
Headache	8 (2.0)	8 (2.0)	16 (2.0)	7 (1.7)	5 (2.6)	15 (7.1)
Tremor	4 (1.0)	10 (2.5)	14 (1.7)	1 (0.24)	0	10 (4.8)
Anxiety	4 (1.0)	1 (0.2)	5 (0.6)	0	0	2 (1.0)
Insomnia	4 (1.0)	0	4 (0.5)	2 (0.5)	2 (1.0)	7 (3.4)
Dysphonia	1 (0.2)	4 (1.0)	5 (0.61)	0	2 (1.0)	0
Respiratory System						
Coughing	2 (0.5)	5 (1.2)	7 (0.9)	5 (1.2)	2 (1.0)	0
Dyspnea	0	5 (1.2)	5 (0.6)	2 (0.5)	5 (2.6)	0

Skin and Appendages Pruritis	4 (1.0)	0	4 (0.5)	1 (0.2)	0	1 (0.5)

*open-label theophylline arm (doses had to be adjusted according to serum levels)

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Experience in children aged 6-12 years with asthma

The safety of FORADIL 12 micrograms twice daily compared to FORADIL 24 micrograms 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 micrograms twice daily (11/171, 6.4%) or FORADIL 12 micrograms twice daily (8/171, 4.7%) than children who received placebo (0/176, 0.0%) experienced serious asthma exacerbations.

For treatment recommendation see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS and 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

8.5 Post-Market Adverse Reactions

Based on its worldwide use involving over 6 million patient-treatment-months since first introduction onto the market in 1990, the adverse event profile of FORADIL is in keeping with that observed in controlled clinical trials.

The following post-marketing events have been reported in patients treated with FORADIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and nutrition disorders: Hypokalemia, hyperglycaemia

Cardiovascular and other medical conditions: Angina pectoris, Electrocardiogram QT prolonged, syncope, blood pressure increased (including hypertension), cardiac arrhythmias e.g. atrial fibrillation, ventricular extrasystoles, tachyarrhythmia

Respiratory, thoracic and mediastinal disorders: Cough

Skin and subcutaneous tissue disorders: Rash

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received in association with the use of FORADIL.

Isolated cases of the following adverse events have also been reported: Hypersensitivity reactions such as severe hypotension, urticaria, angiodema, pruritus, exanthema. Peripheral edema, taste perversion, nausea.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Beta-adrenergic Blockers: beta-adrenergic blockers may weaken or antagonise the effect of FORADIL. Therefore FORADIL should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use.

Short-Acting beta$_2$-agonists: Aerosol bronchodilators of the short-acting adrenergic stimulant type may be used for relief of breakthrough symptoms while using formoterol. However, increasing use of such preparations to control symptoms indicates deterioration of asthma control and the need to reassess the patient's therapy.

Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of FORADIL.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: FORADIL should be administered with extreme caution in patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of formoterol on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QT interval have an increased risk of ventricular arrhythmias.

Corticosteroids, Methylxanthines and Diuretics: Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalemic effect of beta$_2$-agonists. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular. Hypokalemia may increase susceptibility to cardiac arrhythmias in patients treated with digitalis.

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

Other Drugs: Drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistamines, macrolides and tricyclic antidepressants may be associated with QT-interval prolongation and an increased risk of ventricular arrhythmia (see 7 WARNINGS AND PRECAUTIONS).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Formoterol fumarate is a long-acting selective beta$_2$-adrenergic receptor agonist (beta$_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at beta$_2$-receptors than at beta$_1$-receptors. Although beta$_2$- receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the heart, there are also beta$_2$-receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta$_2$-agonists may have cardiac effects.

The pharmacologic effects of beta2-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

10.2 Pharmacodynamics

Formoterol is a potent selective beta$_2$-adrenergic stimulant. It exerts a bronchodilator effect in patients with reversible airways obstruction. It exerts a bronchodilator effect in patients with reversible airways obstruction. The effect sets in rapidly (within 1 to 3 minutes) and is still significant 12 hours after inhalation. At therapeutic doses cardiovascular effects are minor and occur only occasionally.

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

In vitro studies on guinea pig trachea have indicated that racemic formoterol and its (R,R)- and (S,S)-enantiomers are highly selective beta$_2$-adrenoceptor agonists. The (S,S)-enantiomer was 800 to 1,000 times less potent than the (R,R)-enantiomer and did not affect the activity of the (R,R)-enantiomer on tracheal smooth muscle. No pharmacological basis for the use of one of the two enantiomers in preference to the racemic mixture was demonstrated.

In man, formoterol has been shown to be effective in preventing bronchospasm induced by inhaled allergens, exercise, cold air, histamine, or methacholine challenge. The bronchoprotective effect of FORADIL against methacholine provocation has been shown to persist for 12 hours.

In humans, formoterol was more effective than salbutamol at suppressing late phase airway obstruction and increased airway responsiveness to allergen. The clinical significance of these findings is unclear because the long duration of action of formoterol may produce an apparent effect on late phase reactions due to functional antagonism.

Formoterol administered by the Aerolizer inhaler at doses of 12 microgram b.i.d. and 24 microgram b.i.d. was shown objectively to provide rapid onset of bronchodilation in patients with stable COPD that was maintained over at least 12 hours, and which was accompanied by subjective improvement in Quality of Life using the Saint George's Respiratory Questionnaire.

10.3 Pharmacokinetics

As for other inhaled drugs, it is likely that 90% of formoterol administered from an inhaler is swallowed and absorbed from the gastrointestinal tract. Formoterol fumarate acts locally in the lung; plasma levels therefore do not predict therapeutic effect. Systemic levels of formoterol are low or undetectable after inhalation of recommended doses.

Absorption: 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.

Oral doses of up to 300 mcg formoterol fumarate are readily absorbed from the gastrointestinal tract. Peak plasma concentrations of the unchanged substance are reached 0.5 to 1 hour after administration. The absorption of an oral 80 mcg dose is 65% or more.

The pharmacokinetics of formoterol appear linear in the range of oral doses investigated, i.e. 20 to 300 mcg. Repeated oral administration of 40 to 160 mcg daily does not lead to significant accumulation of the drug.

Following inhalation of therapeutic doses, formoterol cannot be detected in the plasma using earlier analytical methods. However, analysis of urinary excretion rates suggests that inhaled formoterol is

rapidly absorbed. The maximum excretion rate after administration of 12 to 96 mcg is reached within 1 to 2 hours of inhalation.

Cumulative urinary excretion of formoterol after administration of the inhalation powder (12 to 24 mcg) and two different aerosol formulations (12 to 96 mcg) showed the amount of formoterol available in the circulation to increase in proportion to the dose.

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

Metabolism: Formoterol is eliminated primarily by metabolism, direct fold glucuronidation being the major pathway of biotransformation. O-demethylation followed by glucuronidation is another pathway.

Elimination: Elimination of formoterol from the circulation seems to be polyphasic; the apparent half-life depends on the time interval considered. 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 feces. After inhalation about 6 to 9% of the dose on average is excreted unchanged in the urine. Renal clearance of formoterol is 150 mL/min.

Detailed Pharmacology

The principal therapeutic effect of formoterol is to relieve and prevent bronchoconstriction by relaxing airway smooth muscle via specific interaction with beta$_2$-adrenoreceptors. Numerous studies have confirmed that formoterol is highly potent and possesses high intrinsic activity and very high affinity at the beta$_2$-adrenoreceptor.

In vitro

In guinea pig isolated trachea, formoterol (pD2 9.29) is approximately 10 times more potent than isoprenaline (pD2 8.57) and 100-fold more potent than salbutamol (pD2 7.13) as an airway smooth muscle relaxant. In terms of relaxant potency and efficacy on human isolated bronchi at resting tone or pre-contracted with acetylcholine, formoterol displays higher intrinsic activity than the partial agonists salbutamol and salmeterol, causing greater than 80% relaxation even under induced tone. Formoterol displays less intrinsic activity than the full agonist isoprenaline (Table 4).

Table 4- Potency (EC_{50}) and efficacy (E_{max}) of selected agonists on human bronchus *in vitro*						
Agonist	Basal Tone			1mM acetylcholine		
	EC_{50}	E_{max}	I.A.	EC_{50}	E_{max}	I.A.
Isoprenaline	7.31±0.12	98±0.4	1.00	6.56±0.13	85±3.7	1.00
Adrenaline	6.85±0.12	95±1.1	0.97	6.29±0.10 b	87±3.5 b	1.02
Formoterol	9.63±0.11	94±1.2 a	0.96	8.74±0.19 b	71±6.9 b	0.84
Salbutamol	7.12±0.17	83±2.4 a	0.85	-	55±6.5 a,b	0.64
Salmeterol	7.96±0.19	70±6.0 a	0.71	-	53±6.0 a,b	0.62

Full agonists (intrinsic activity = 1) are expected to cause 100% relaxation (E_{max} =100) of the maximal effect elicited by theophylline (3mM). Intrinsic activity (I.A.) is defined as [E_{max} (drug)/ E_{max} isoprenaline] under basal tone and acetylcholine induced tone.

Mean data ± SEM of n=10-15; [a] $p<0.05$ compared with isoprenaline, [b] $p<0.05$ compared with basal.

Pre-incubation of human bronchi with adrenaline (full agonist) or formoterol (very strong partial agonist) caused a slight rightward displacement of a second dose response curve to adrenaline. In contrast, salmeterol caused a dose-related suppression of responses to adrenaline which reflect non-competitive antagonism. No such competitive activity was observed with formoterol.

Formoterol has a very high absolute value of binding affinity for the $beta_2$-adrenoreceptor (pK_D: formoterol 8.12 vs. salbutamol 6.44). The terbutaline analog delta pK_D value of 330 (delta pK_D $beta_1$ vs. $beta_2$ binding = 2.52) confirms that formoterol is an order of magnitude more selective for $beta_2$-adrenoreceptors.

Formoterol has a very rapid onset and long duration of action *in vitro*. Formoterol has also been shown to "reassert" relaxation. Guinea pig trachea was pre-contracted with carbachol and then relaxed with either formoterol, salmeterol or salbutamol. This relaxation was then pharmacologically antagonized by the addition of sotalol. However, when this antagonist was washed out, the activity of formoterol was "reasserted", suggesting retention within the tissue, whereas salbutamol did not show this effect. A longer duration of action *in vitro* and the "reassertion" effect are properties consistent with a lipophilic beta-adrenoreceptor agonist.

The mechanism responsible for the long duration of action of formoterol has not been unequivocally established. However, it is likely that the mode of action of long acting beta-adrenoreceptor agonists is related to their plasmalemma diffusion microkinetics, i.e., their behaviour at the water/membrane lipid interface in the immediate vicinity of the $beta_2$-adrenoreceptor.

In vivo

In-vivo bronchodilation

In keeping with its very high potency and beta$_2$-adrenoreceptor selectivity, formoterol was a highly effective bronchodilator in *in vivo* animal studies. This bronchodilator activity, measured as suppression of bronchoconstriction induced by acetylcholine, serotonin or histamine, was evident in cats, guinea pigs and dogs after oral or intravenous administration. A longer duration of action and very high potency was also evident in guinea pigs and dogs after aerosol administration of formoterol compared to reference beta-adrenoreceptor agonist compounds. Formoterol administered as a 300 mcg/mL aerosol to dogs suppressed antigen induced bronchospasm for as long as 24 hours.

Effects on mediator release

In vivo cutaneous anaphylactic response

Formoterol administered orally or intravenously inhibits IgE mediated cutaneous anaphylactic responses in the rat and guinea pig. In rats the profile is similar to terbutaline in time of onset and maximum effect at 2 hours, but formoterol has a longer duration of action. Formoterol also inhibits histamine induced pulmonary edema and arachidonic acid induced mouse ear edema, indicating a direct effect of formoterol on microvascular permeability. The effect of formoterol on mediator release was observed at lower concentrations compared with other beta$_2$-adrenergic agents.

11 STORAGE, STABILITY AND DISPOSAL

Protect from heat (i.e., store between 15-25^{o}C) and humidity.

12 SPECIAL HANDLING INSTRUCTIONS

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 capsule made of edible gelatin is not harmful if ingested.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

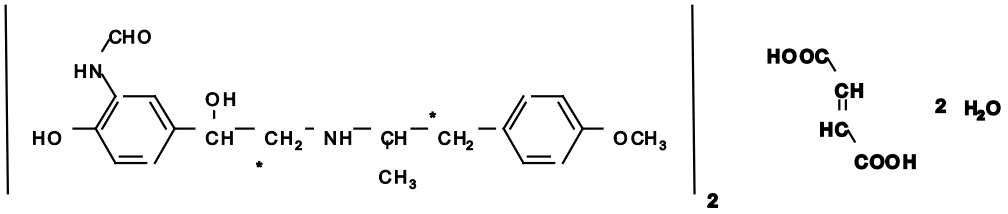
Proper name: Formoterol fumarate

Chemical name: (±)-2'-Hydroxy-5'-[(RS)-1-hydroxy-2-[[(RS)-*p*-methoxy- *α* -methylphenethyl]-amino]ethyl]- formanilide fumarate dihydrate

Molecular formula and molecular mass: $(C_{19}H_{24}N_2O_4)_2 \bullet C_4H_4O_4 \bullet 2\ H_2O$

840.9 (344.4 free base)

Structural formula:



Physicochemical properties:

Description: Odourless, white to yellowish crystalline powder.

Solubility: Quantity dissolved

Solvent	(mg/mL)
Glacial Acetic Acid	149
Methanol	73.5
Absolute ethanol	4.88
Water	0.980

Melting Point: Melts at approximately 138°C with decomposition.

pK_a values: 7.82, 8.54

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Asthma:

The efficacy of formoterol dry powder was evaluated in controlled clinical studies using 12 mcg and 24 mcg b.i.d. in adults and children. Formoterol showed superior efficacy compared to salbutamol dry powder (400 mcg b.i.d.). Formoterol significantly improved lung function, reduced nocturnal and daytime asthma symptoms and reduced the need for additional short-acting relief bronchodilators.

Chronic Obstructive Pulmonary Disease:

The efficacy of formoterol dry powder was evaluated in two placebo-controlled and comparator-controlled clinical studies.

14.2 Study Results

Asthma

Adults: sustained bronchodilator and bronchoprotective effect of formoterol inhaled twice daily for six months in moderate asthma

A 6-month randomized double-blind trial was conducted in 271 patients with moderate asthma to compare the effect on bronchial hyperresponsiveness (as measured by the methacholine challenge) of three treatments; twice daily formoterol dry powder capsules (12 mcg b.i.d.), four times daily salbutamol dry powder capsules (200 mcg q.i.d.), or salbutamol MDI on-demand. All patients were taking inhaled corticosteroids (400 to 1200 mcg beclomethasone or equivalent). Mean baseline FEV_1 was 2.73 L (80% of predicted). Mean age was 36. Geometric means of PC_{20} were comparable between treatment groups, at baseline (0.7 to 0.8 mg/mL), but increased during double-blind period to values between 4.1 and 5.1 in the formoterol group, 2.6 and 3.6 in the regular salbutamol group, and 1.3 and 1.7 in the on-demand salbutamol group. Formoterol achieved significantly better protection against methacholine-induced bronchial hyperreactivity at the beginning of treatment, at 3 months, at 6 months, and achieved significantly better control of the disease as measured by spirometry, peak flow, symptom scores, and rescue medication compared to on-demand salbutamol. In all treatment groups there was no rebound effect measured 2 days after cessation of treatment: (PC_{20} between 2.0 and 2.2 mg/mL). Formoterol treated patients experienced fewer exacerbation days compared to patients treated with on-demand salbutamol. A similar trend between Formoterol and regular salbutamol did not reach statistical significance.

Children: sustained bronchodilator and bronchoprotective effect of formoterol inhaled twice daily for twelve months in asthma

A 12-month, double-blind, placebo-controlled trial was conducted in 518 children (aged 5 - 12 years) with asthma to determine if 12 mcg or 24 mcg of formoterol dry powder capsules for inhalation delivered by a single-dose breath actuated inhaler (Aerolizer) administered b.i.d. were superior to placebo with respect to lung function measurements over a 12-month period.

Patients had baseline FEV_1 of 50 - 85% of normal and 15% increase in FEV_1 within 30 mins after inhaling 200 mcg salbutamol.

The area under the FEV_1 curve measured over 12 hours was significantly greater than placebo for both formoterol 12 mcg b.i.d. and 24 mcg b.i.d after twelve weeks of treatment. No difference was seen between the doses. Similar results were seen after the first dose and after 12 months treatment, for FEF 25-75%, FVC for the 24 mcg dose and for morning and evening premedication PEFR. Symptom scores were significantly lower than placebo in the 12 mcg b.i.d.group but not in the 24 mcg b.i.d group at the three month efficacy time point, but were no longer significant at 12 months for either dose. Rescue medication was used significantly less at night-time for both formoterol doses, but was only significantly less for the lower dose during the night-time over the twelve month period.

Non-pulmonary Effects

Potentially serious ECG changes (such as increased QTc interval) and hypokalemia may result from $beta_2$-agonist therapy. Although clinically not significant, a small increase in QTc interval and/or decrease in serum potassium has been reported at therapeutic doses of formoterol. The effects of single doses of formoterol at 12 to 96 mcg were studied in 22 adult asthmatics, all of whom were receiving inhaled corticosteroids and an inhaled short-acting $beta_2$-agonist prior to entering the trial. The number of patients whose longest measured QT_c in this trial was >440 msec was greater for placebo (3 patients) than it was for formoterol 12 mcg (no patient), 24 mcg (2 patients), and 48 mcg (2 patients). Five patients treated with formoterol 96 mcg showed QT_c prolongations >440 msec. Six patients had clinically meaningful ($[K^+]$ <3.2 mmol/L) hypokalemia at 96 mcg, compared with one each at 12 and 48 mcg.

Chronic Obstructive Pulmonary Disease

A 12-week randomized double-blind trial was conducted in 780 patients with COPD to assess the efficacy of inhaled formoterol fumarate dry powder capsules (12 mcg b.i.d. and 24 mcg b.i.d.) compared with placebo or ipratropium bromide MDI (40 mcg q.i.d.). Patients were male or female out-patients over or equal to 40 years old. Their FEV_1 was expected to be less than 70% of the predicted value and at least 0.75 litres, with the FEV_1/VC being less than 88% for men and less than 89% for women. Fomoterol at both 24 mcg and 12 mcg b.i.d. produced statistically and clinically significant improvements in lung function, as measured by FEV_1 area under the curve, when compared to placebo after 12 weeks of treatment. The estimated improvement was 194 mL and 223 mL for 24 mcg and 12 mcg b.i.d., respectively. Formoterol was also statistically significant when compared to ipratropium bromide.

Both doses of formoterol, when compared to placebo, produced statistically and clinically significant improvement of this variable in both reversible and irreversible sub-groups of patients. (Reversibility is defined as ≥15% increase in forced expiratory volume in one second (FEV_1) 30 minutes after inhalation of 200 mcg salbutamol). For reversible patients the improvement seen was 244 mL and 241 mL for formoterol 24 mcg and 12 mcg b.i.d., respectively. For irreversible patients the improvement seen was 137 mL and 213 mL for formoterol 24 mcg and 12 mcg b.i.d., respectively.

Formoterol (24 mcg and 12 mcg b.i.d.) when compared to placebo showed statistically significant improvements in all the lung function measurements: FEV_1 AUC on day 1 of treatment, FEV_1 at each time-point over 12 hours, IVC, FVC AUC and morning pre-medication PEF. Statistically significant improvements were also seen in clinical measures: total score on the patient diary, number of puffs of rescue medication and the percentage of bad days. Quality of Life, as measured by the St. George's Respiratory Questionaire (SGRQ), was both statistically and clinically significantly improved in all areas (total, symptoms, activity and impacts) for formoterol (12 mcg b.i.d.) when compared to placebo with

statistically significant improvements for the 24 mcg b.i.d. dose for the total, symptoms and activity scores.

The primary objective of the 12-month randomized between patient trial was to assess the efficacy of inhaled formoterol fumarate dry powder capsules (12 mcg b.i.d. and 24 mcg b.i.d.) compared with placebo with respect to FEV_1 AUC (after 12 weeks). The secondary objective was to compare formoterol with placebo (with respect to FEV_1 AUC at 6 and 12 months) and with oral SR theophylline after 3, 6 and 12 months (FEV_1 pre-dose at all visits and post-dose after 3, 6 and 12 months). The two formoterol and the placebo groups were compared in a double-blind mode, while the theophylline group was open-label. A total of 854 male or female out-patients over or equal to 40 years old patients with COPD were randomized. Their FEV_1 was expected to be less than 70% of the predicted value and at least 0.75 litres, with the FEV_1/VC being less than 88% for men and less than 89% for women.

Formoterol at both 24 mcg and 12 mcg b.i.d. produced statistically and clinically significant improvements in lung function, as measured by FEV_1 area under the curve, when compared to placebo after 12 weeks of treatment. The estimated improvement was 208 mL and 200 mL for 24 mcg and 12 mcg b.i.d., respectively. Formoterol was also statistically significant when compared to theophylline. Both doses of formoterol, when compared to placebo, produced statistically and clinically significant improvement of this variable in both reversible and irreversible sub-groups of patients. (Reversibility is defined as ≥15% increase in forced expiratory volume in one second (FEV_1) 30 minutes after inhalation of 200 mcg salbutamol). For reversible patients the improvement seen was 271 mL and 331 mL for formoterol 24 mcg and 12 mcg b.i.d., respectively. For irreversible patients the improvement seen was 166 mL and 109 mL for formoterol 24 mcg and 12 mcg b.i.d., respectively.

Formoterol (24 mcg and 12 mcg b.i.d.) when compared to placebo showed statistically significant improvements in the other lung function measurements: FEV_1 AUC after 6 and 12 months of treatment, FEV_1 at each time-point over 12 hours, FVC AUC and morning pre-medication PEF after 3, 6 and 12 months of treatment. Statistically significant improvements between both doses of formoterol when compared with placebo were also seen in the number of puffs of rescue medication taken. Quality of Life, as measured by the St. George's Respiratory Questionnaire (SGRQ), was statistically significantly improved in all areas (total, symptoms, activity and impacts) for formoterol (12 mcg b.i.d.) when compared to placebo after 6 months of treatment, and for both impact and total scores for 24 mcg b.i.d. Clinically relevant improvement in the symptoms scores were seen in the formoterol 12 mcg b.i.d. treatment group at both 6 and 12 months and in the impacts score for the formoterol 24 mcg b.i.d. treatment group at 12 months.

In conclusion, FORADIL administered by the Aerolizer at doses of 12 mcg b.i.d. and 24 mcg b.i.d. provides rapid onset of bronchodilation in patients with stable COPD that was maintained over at least 12 hours.

Since the bronchodilator effect of FORADIL is still significant 12 hours after inhalation, twice-daily maintenance therapy controls bronchoconstriction associated with chronic conditions both during the day and at night.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Single dose toxicity of formoterol is low to moderate with some interspecies variability.

Table 5 - Acute toxicity of Formoterol (min. lethal doses in mg/kg)

	Rats male/female	Mice male/female	Chinese Hamsters (male and female)	Dogs (male only)
P.O.	889/3000	5000/6500	100	3000
I.V.	80/80	61/61		
S.C.	722/722	508/610		
I.P.	141/169	169/169		
			parenteral studies not conducted	

Long-Term Toxicity

Cardiostimulation and cardiotoxicity of formoterol were demonstrated in peroral and parenteral subchronic and chronic toxicity studies lasting up to two years in rodents and up to one year in dogs. Effects were seen at dose levels starting at 0.003 mg/kg in the dog and at 0.3 mg/kg in the rat. Clinically, an increase in heart rate was noted and morphologically, signs of minute focal myocardial degeneration. These adverse effects appeared to occur with other beta$_2$-adrenergic agonists and were clearly dose-dependent.

Inhalation Toxicity

Therapeutically, formoterol will be administered by the inhalation route which results in lower systemic exposure for the desired pulmonary effect. Results for inhalation toxicity studies with formoterol are shown in Table 6. Long-term toxicity studies were performed only with orally administered formoterol. Since formoterol is not metabolized in the lung, these studies are valid for assessing the safety of inhalation exposure.

In early inhalation toxicity studies using aerosols of micronized formoterol in air propellant atmospheres, rats tolerated doses up to 22 mg/kg upon discontinuous exposure. Further studies were done with metered dose aerosols, both solution and suspension (see Table 6). Administration of 2.4 mg/kg to dogs in a single session resulted in tachycardia, but daily doses of 1.2 mg/kg for 28 days or 600 mg for 3 months did not induce cardiotoxicity, even though an inhaled dose is pharmacologically active for up to 24 hours.

Subsequent experiments used a 1 to 1000 formoterol/lactose formulation comparable to the dry powder inhalation capsules, and included 3-month inhalation studies in rats and dogs at doses up to 33

mg/kg (nominal) and 15 mg/kg, respectively. The results showed mainly mild alterations, such as increased body and heart weights in rats and raised heart rates in dogs, which were related to pharmacological action rather than to toxicity; however, dogs displayed slight to moderate myocardial fibrosis at the top dose.

Table 6 - Inhalation Toxicology with Formoterol

	Duration (weeks)	Daily Dose		Major Findings
		in mg/L air + propellant	by weight	
Rat	acute *	0.3 - 5.7	~5.8 - 110 mg/kg	MLD = 0.81 mg/L (~16 mg/kg)
Rat	acute *	0.26 - 6.1	~0.9; 4.4; 21.9 mg/kg	Non-lethal at 6.1 mg/L
Rat	acute #	0.007 - 0.043	0.89 - 5.7 mg/kg	Well-tolerated up to 7 days
Rat	acute ¤	3.5	43 - 53 mg/kg	No deaths
Rat	2 *	0.17 - 6.6	~0.6; 2.9; 24 mg/kg	NOEL 0.6 mg/kg
Rat	13 *	0.01 - 0.23	0; 2.9; 24 mg/kg	Cardiotoxicity; NOEL 0.14 mg/kg
Rat	13 #		0.03; 0.15; 0.44 mg/kg	Body weight increase
Rat	13 ¤	0.07; 0.17; 0.73	~3; 10; 33 mg/kg	Pharmacological effects: body and heart weight increased; glucose decreased
Dog	acute *		2.4 mg	Non lethal
Dog	acute #		2.4 mg	Well-tolerated
Dog	4 §		1.2 mg/kg	No marked effects
Dog	13 §		600 mg	No marked effects
Dog	13 #		600 mg	No marked effects
Dog	13 ¤		1.5; 5; 15 mg/kg	Pharmacological effects (heart rate) Cardiotoxic at 15 mg/kg

* = micronized formoterol in air/propellant

§ = formoterol solution aerosol

= formoterol suspension aerosol

NOEL = No Observable Effect Level

¤ = formoterol / lactose dry powder (1/1000)

MLD = Minimum Lethal Dose

Mutagenicity Studies

No mutagenic effects were found in any of the mutagenicity tests conducted with formoterol covering a broad range of experimental end-points. *In vitro* DNA repair was studied in *B. subtilis*, rat hepatocytes and human fibroblast, reverse mutation in *E. coli* and *S. typhimurium*, point mutation in *typhimurium* and Chinese Hamster cells, and a quantitative assay of malignant cell transformation (BALB/3T3). *In vivo* chromosome studies and a micronucleus test were also done.

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 aging 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 $beta_2$-adrenergic drugs. Increased incidences of ovarian cysts and benign granulosa/theca cell tumours were also seen; beta-agonists are known to have effects on the ovary in rats 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 and Developmental Toxicology:

In the two fertility studies performed in sexually mature male and female rats, no impairment of fertility and general reproductive performance and no embryo- or feto-toxicity was noted. No impairment of fertility or effect on early embryonic development was observed at oral doses up to 3 mg/kg administered orally to rats (approximately 1200 times the maximum recommended daily inhalation powder dose in human on a mcg/m^2 basis).

In peri- and post-natal study in rats, a decreased survival rate of pups was noted. Because of this finding, a nursing study was also conducted. Litters from treated dams were nursed by untreated dams and vice-versa. The results suggest that mortality of pups was associated with maternal treatment during the peri-natal period. In this context, the proven passage of formoterol into milk of lactating rats is of importance. "Wavy ribs" were noted in fetuses in the rat teratology study and could be explained as the consequence of an incongruity between the force of (e.g. cervical and abdominal) muscular contractions and a delay in ossification. None of the pups examined on day 21 of weaning had this finding. In the rabbit teratology study with formoterol, the only finding was a decrease in the number of viable fetuses per litter at the high dose of 500 mg/kg.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrFORADIL®

formoterol fumarate dry powder capsules for inhalation

Read this carefully before you start taking **FORADIL®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FORADIL**.

Serious Warnings and Precautions

SERIOUS WARNING FOR ASTHMA PATIENTS TAKING FORADIL:

FORADIL increases the risk of asthma-related death. It may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. Therefore,

- FORADIL must **only** be used as an **add-on** therapy when your inhaled corticosteroid does not adequately control your asthma symptoms
- FORADIL must be used together with an inhaled corticosteroid
- The dose of FORADIL may be reduced (from two capsules twice daily to one capsule twice daily) or discontinued by your physician when your asthma is assessed as adequately under control.
- It is extremely important to make sure that children 6 to 18 years of age take both FORADIL and an inhaled corticosteroid. If this can not be guaranteed, speak to the prescribing physician as a combination product may be required.

For any concerns regarding the use of FORADIL, consult with your physician.

What is FORADIL used for?

Asthma (patient 6 years old and older):

FORADIL is used only as add-on therapy to an inhaled corticosteroid when an inhaled corticosteroid cannot control the asthma by itself.

FORADIL is a long-acting beta$_2$-agonist and **should not be used to provide relief for a sudden attack of breathlessness.**

Chronic Obstructive Pulmonary Disease (COPD):

FORADIL is used for the management of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema in adults.

How does FORADIL work?

- **FORADIL** belongs to a drug class known as a long-acting bronchodilator.
- FORADIL opens air ways in the lungs to make breathing easier, and keep them open and relaxed for about 12 hours.
- FORADIL must be used with an inhaled corticosteroid to reduce the inflammation of the lungs due to asthma.

What are the ingredients in FORADIL?

Medicinal ingredients: formoterol fumarate.

Non-medicinal ingredients: gelatin, lactose monohydrate, shellac glaze 45%, black iron oxide, isopropyl alcohol, n-butyl alcohol, propylene glycole, purified water , dehydrated ethanol, ammonium hydroxide 28%

FORADIL comes in the following dosage forms:

FORADIL comes as gelatin capsules containing a dry powder. The dry powder is INHALED into the lungs using the inhaler provided. FORADIL comes in blister packs containing 60 capsules. Each capsule of FORADIL contains 12 micrograms of *formoterol fumarate*

Do not use FORADIL if:

- You are not being treated with an inhaled corticosteroid (ICS) for your asthma. The ICS decreases the inflammation in your lungs while FORADIL opens the airways. Do not take FORADIL without an ICS
- you have heart problems
- you are allergic to formoterol fumarate or any of the nonmedicinal ingredients in FORADIL
- you are allergic to lactose (milk sugar)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FORADIL. Talk about any health conditions or problems you may have, including if:

- You have significantly worsening asthma
- You have health problems now or have had health problems in the past, especially heart disease, diabetes, overactive thyroid.
- If you have an aneurysm (area where an artery is swollen like a sack because the wall of the artery is weak).
- You have a heart disorder, such as rapid or irregular heart beat or an abnormal electrical signal called “prolongation of the QT interval”.
- You have high blood pressure.
- If you have pheochromocytoma (a tumor of the adrenal gland that can affect blood pressure)
- You are pregnant, plan to become pregnant or are breast-feeding

Other warnings you should know about:

Driving and Operating Machinery: Do not drive or operate machinery if you experience dizziness while taking FORADIL

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FORADIL:

- Short-Acting beta-agonists
- Medications used to treat depression or sad mood (monoamine oxidase inhibitors and tricyclic antidepressants)
- Antihistamines
- Water pills (diuretics)
- Beta-blockers for high blood pressure and certain eye drops for the treatment of glaucoma
- Steroids such as corticosteroids
- Drugs containing quinidine, disopyramide, procainamide, phenothiazine or xanthine derivatives (theophylline or aminophylline)
- Macrolide antibiotics (e.g. erythromycin; azithromycin; clarithromycin)
- Inhaled anaesthetics such as halogenated hydrocarbons (e.g. halothane), used during surgery. Inform your doctor that you use FORADIL if you are to have surgery under anaesthesia.

How to take FORADIL Aerolizer:

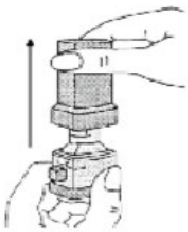
- It is very important that you take FORADIL exactly as your doctor tells you.
- Inhale the contents of the capsules using the Aerolizer inhaler. Do not swallow the capsules.
- Children 6 years of age or older should only use FORADIL if they are able to handle the inhaler correctly. They should only use the inhaler with the help of an adult.
- If the relief of your asthma is not as good as usual or does not last as long as usual, tell your doctor right away. A change from "usual" includes more wheezing, coughing, tightness or shortness of breath. More frequent severe asthma symptoms can occur in children 6-12 years old. Monitor your child's use of all asthma related medications and their response to FORADIL carefully.
- If your symptoms are waking you up at night tell your doctor right away. Your doctor may adjust your treatment.
- You may need emergency treatment if your asthma symptoms are not relieved, despite taking all your prescribed medications, and after resting for an hour.
- You should not use FORADIL to treat sudden asthma attacks. A short-acting bronchodilator (also known as a quick reliever e.g. salbutamol) should also be used when you have a sudden attack of shortness of breath, tightness, coughing and wheezing.
- If you are using more of your short-acting bronchodilating medication or if you feel that it is less effective tell your doctor right away. Your doctor may adjust your treatment.

You must continue to regularly take the anti-inflammatory medications (e.g., inhaled steroids) your doctor has prescribed. Do not change or stop any of your medicines to control or treat your breathing problems, including your inhaled corticosteroid. Your doctor will adjust your medicines as needed.

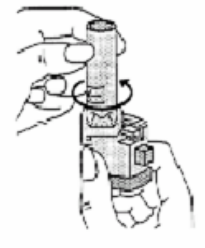
Your anti-inflammatory medications and FORADIL are designed to act together to best treat your asthmatic condition. Even though you feel better, do not stop or reduce your doses of FORADIL or your anti-inflammatory medications.
For children 6-18 years of age, treatment with a combination product containing an inhaled corticosteroid and long-acting bronchodilator is recommended, except in case where a separate inhaled corticosteroid and long-acting bronchodilator are required.
FORADIL should not be used with another long-acting bronchodilator alone (e.g. Oxeze or Serevent) or in combination with a steroid (e.g., Symbicort, Advair).

How do I use the FORADIL inhaler and capsules?

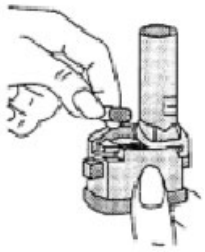
1. Pull off cap



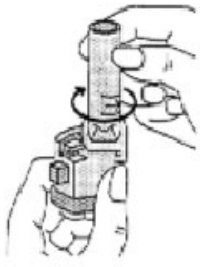
2.To open, hold base of the inhaler firmly and turn the mouthpiece in the direction of the arrow.



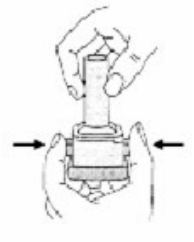
3.Remove the capsule from the blister pack. It is important to keep the capsule in the blister pack until you are ready to use it. Place the capsule in the capsule shaped compartment in the base of the inhaler.



4.Return the mouthpiece to the closed position.



5.Keeping the inhaler upright, firmly squeeze the two blue buttons fully **only once**. This will pierce the capsule. Release the buttons. Although the capsule is now pierced, the powder will not be released until you inhale it.



Please note that the capsule might splinter at this step and small fragments of gelatin might reach your mouth and throat. This gelatin is edible and is therefore not harmful. You can minimize the tendency of the capsule splintering by:

- *piercing the capsule only once*
- *keeping the capsules stored in a dry place at room temperature*
- *keeping the capsule in the blister pack until you are ready to use it.*

6.Breathe out fully.

7.Place the mouthpiece in your mouth and tilt your head slightly backward. Close your lips around the mouthpiece and breathe in steadily as deeply as you can. As you breathe in, you will inhale the medication into your lungs.

You should hear a whirring noise as you breathe in because inhalation causes the capsule to spin around in the inhaler. ***Please note*** *if you do not hear the whirring noise, the capsule may be stuck in the capsule-shaped compartment. If this occurs, re-open the inhaler carefully and pry the capsule out. You cannot loosen the capsule by repeatedly pressing the buttons.*

8. If you have heard the whirring noise, **hold your breath** for as long as you comfortably can while removing the inhaler from your mouth. Then breathe out.

9. After use, open the inhaler. Check that the capsule is empty. If it is not close the inhaler and re-inhale following steps 6, 7 and 8. Remove the empty capsule. Close the mouthpiece. Replace the cap.

How to clean the inhaler:

To remove any powder residues, wipe the mouthpiece and capsule compartment with a **dry** cloth or a small, soft, clean brush.

Usual dose:

ASTHMA:

You or your child will always be prescribed FORADIL in addition to an inhaled corticosteroid.

Adults: The regular dose of FORADIL for adults, is 1 or 2 capsules twice a day, once in the morning and again in the evening.

You should not use more than 2 capsules twice daily.

The dose of FORADIL may be reduced (from two capsules twice daily to one capsule twice daily) or discontinued by your physician when your asthma is assessed as adequately under control.

Children: The recommended dose for **children** 6 years of age or older is 1 capsule twice a day. The severity of asthma changes with age. Your child should therefore be periodically re-examined by a physician.

Your child should not use more than 1 capsule twice daily.

It is extremely important to make sure that children 6 to 18 years of age take both FORADIL and an inhaled corticosteroid. If this can not be guaranteed, speak to the prescribing physician as a combination product may be required.

COPD: The regular dose for adults, including elderly patients, is 1 or 2 capsules twice a day, once in the morning and again in the evening. You should not use more than 2 capsules twice daily.

FORADIL should not be taken more than twice daily.

Overdose:

If you develop nausea and/or vomiting, shakiness, headache, dizziness (possible symptoms of high blood pressure), fast or irregular heartbeat, or sleepiness, your dose of FORADIL may be too high. Seek immediate medical attention.

If you think you, or a person you are caring for, have taken too much FORADIL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

FORADIL should not be used more often than twice a day. If you forget to take a dose, take it as soon as possible. However, if it is almost time for your next dose, do not take the missed one, just go back to your regular dosing schedule. Never take a double dose.

What are possible side effects from using FORADIL?

These are not all the possible side effects you may feel when taking FORADIL. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- tremor,
- headache,
- dry mouth, or irritation of the mouth or throat.
- muscle cramps and pain,
- agitation, feeling nervous or tired,
- difficulty sleeping.

You should keep track of any side effects and if they persist, notify your doctor on your next visit.

FORADIL can cause abnormal blood test results. Your doctor will decide when to preform blood tests and will interpret the results.

If you feel you are getting breathless or wheezy while you are using FORADIL, you should continue to use it, but see your doctor as soon as possible in case you need another medicine. If this occurs immediately after a dose, stop taking the drug and seek immediate emergency medical attention.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Bronchospasm with wheezing or coughing and difficulty in breathing, immediately after taking your dose			**X**
Serious Asthma Attacks: severe			**X**

increase in shortness of breath, cough, wheezing, or chest tightness which can result in hospitalization			
RARE			
Decreased level of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		**X**	
VERY RARE			
Fast and irregular heartbeat			**X**
Angina Pectoris: Crushing pain in chest			**X**
Allergic Reaction: fainting, due to low blood pressure, rash, or itching, or swelling of the face, mouth or throat			**X**
High Blood Pressure: headache and dizziness			**X**
Increased Blood Sugar: frequent urination, thirst, and hunger		**X**	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep this medication at room temperature, in a dry place. Your car or the bathroom are not good choices.

The capsules should be removed from the blister pack just before use. Keep this medicine out of the reach of children because it may harm them. Do not use FORADIL after the expiry date marked on the carton.

If you want more information about FORADIL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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