BECLOMETASONE DIPROPIONATE FORMOTEROL FUMARATE DIHYDRATE

FOSTER®

100 mcg /6 mcg per actuation
Metered Dose Inhaler
ANTIASTHMA

FORMULATION
Each actuation/metered dose (ex-valve) contains :
Beclometasone dipropionate (corresponding to 84.6 mcg as deliverable dose).....100 mcg
Formoterol fumarate dihydrate (corresponding to 5 mcg as deliverable dose).....6 mcg

PHARMACOLOGY

PHARMACOKINETICS
Beclometasone is stated to be readily absorbed from sites of local application, and rapidly distributed to all body tissues. It is metabolized principally in the liver, but also in other tissues including gastrointestinal tract and lung; enzymatic hydrolysis rapidly produces the monopropionate (which has some glucocorticoid activity), and more slowly, the free alcohol, which is virtually devoid of activity. Only a small proportion of an absorbed dose is excreted in urine, the remainder being excreted in the feces mainly as metabolites.
Inhaled formoterol is rapidly absorbed. It is largely metabolized by glucuronidation and o-demethylation, with about 10% being excreted as unchanged drug. The terminal elimination half-life after inhalation is estimated to be 8 hours.

PHARMACODYNAMICS
Beclomethasone dipropionate given by inhalation at recommended doses has a glucocorticoid antiinflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.
Formoterol is a selective beta$_2$-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

CLINICAL RESULTS

ASTHMA

Clinical efficacy for maintenance therapy
In clinical trials in adults, the addition of formoterol to beclometasone dipropionate improved asthma symptoms and lung function and reduced exacerbations.
In a 24-week study the effect on lung function of Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) was at least equal to that of the free combination of beclometasone dipropionate and formoterol, and exceeded that of beclometasone dipropionate alone.

Clinical efficacy for maintenance and reliever therapy
In a 48-week parallel group study involving 1701 asthma patients, the efficacy of Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) administered as maintenance (1 inhalation BID) and reliever therapy (up to a total of 8 puffs per day) was compared to Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) administered as maintenance therapy (1 inhalation BID) plus as needed salbutamol, in adult patients with uncontrolled moderate to severe asthma. The results demonstrated that Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) used as maintenance and reliever therapy significantly prolonged the time to first severe exacerbation (*) when compared with Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) used as maintenance plus as needed salbutamol ($p < 0.001$ for both ITT and PP population). The rate of severe asthma exacerbations per patients/year, was significantly reduced in the maintenance and reliever therapy group compared to salbutamol group: 0.1476 vs. 0.2239 respectively (statistically significant reduction: $p < 0.001$). Patients in the Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) maintenance and reliever group achieved a clinically meaningful improvement in asthma control. The mean number of inhalations/day of reliever medication and the proportion of patients using reliever medication decreased similarly in both groups.
Note*: severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room treatment, or resulting in the need for systemic steroids for more than 3 days
In another clinical study, a single dose of Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) 100/6 mcg provided a quick bronchodilation effect and a rapid relief from dyspnea symptoms similar to that of salbutamol 200 mcg/dose in asthmatic patients when metacholine challenge is used to induce bronchocostriction.

COPD
In two 48-weeks studies, the effects on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with severe COPD ($30\% < FEV1\% < 50\%$) was evaluated.
One pivotal trial showed a significant improvement in lung function (primary endpoint change in pre-dose FEV1) compared to formoterol after 12 weeks of treatment (adjusted mean difference between Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) and formoterol: 69 ml) as well as at each clinic visit during the whole treatment period (48 weeks). The study demonstrated that the mean number of exacerbations per patient/year (exacerbation rate, co-primary endpoint) was statistically significantly reduced with Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) as compared with formoterol treatment (adjusted mean rate 0.80 compared with 1.12 in the formoterol group, adjusted ratio 0.72, $p < 0.001$) over 48 weeks treatment period in a total of 1199 patients with severe COPD. In addition, Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) statistically significantly prolonged the time to first exacerbation compared to formoterol. The superiority of Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) versus formoterol was also confirmed in terms of exacerbation rate in subgroups of patients taking (around 50% in each treatment arm) or not Tiotropium Bromide as concomitant medication.
The other pivotal study, which was a three arm, randomised, parallel group study in 718 patients, confirmed the superiority of Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) versus formoterol treatment in terms of change in pre-dose FEV1 at the end of treatment (48 weeks) and demonstrated the non-inferiority of Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) compared to budesonide/formoterol fixed dose combination on the same parameter.

INDICATIONS

ASTHMA
Beclomethasone dipropionate/Formoterol fumarate dihydrate (Foster) is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting beta$_2$-agonist) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled rapid-acting beta$_2$-agonist or
- patients already adequately controlled on both inhaled corticosteroids and long-acting beta$_2$-agonists.

COPD
Symptomatic treatment of patients with severe COPD (FEV1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

CONTRAINDICATIONS
Contraindicated in patients with hypersensitivity to any component of this product.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The drug should be used with caution (which may include monitoring) in patients with cardiac arrhythmias, especially third degree atrioventricular block and tachyarrhythmias (accelerated and/or irregular heart beat), idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, severe heart disease, particularly acute myocardial infarction, ischaemic heart disease, congestive heart failure, occlusive vascular diseases, particularly arteriosclerosis, arterial hypertension and aneurysm.
Caution should also be observed when treating patients with known or suspected prolongation of the QTc interval, either congenital or drug induced (QTc > 0.44 seconds). Formoterol itself may induce prolongation of the QTc interval.
Caution is also required when the drug is used by patients with thyrotoxicosis, diabetes mellitus, phaeochromocytoma and untreated hypokalaemia.
Potentially serious hypokalaemia may result from beta$_2$-agonist therapy. Particular caution is advised in severe asthma as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other drugs which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics. Caution is also recommended in unstable asthma when a number of "rescue" bronchodilators may be used. It is recommended that serum potassium levels are monitored in such situations.
The inhalation of formoterol may cause a rise in blood glucose levels. Therefore blood glucose should be closely monitored in patients with diabetes.
If anaesthesia with halogenated anaesthetics is planned, it should be ensured that the drug is not administered for at least 12 hours before the start of anaesthesia as there is a risk of cardiac arrhythmias.
As with all inhaled medication containing corticosteroids, the drug should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.
It is recommended that treatment with the drug should not be stopped abruptly.
If patients find the treatment ineffective medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. Sudden and progressive deterioration in control of asthma or COPD is potentially life- threatening and the patient should undergo urgent medical assessment. Consideration should be given to the need for increased treatment with corticosteroids, either inhaled or oral therapy, or antibiotic treatment if an infection is suspected.
Patients should not be initiated on the drug during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. Serious asthma-related adverse events and exacerbations may occur during treatment with the drug. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on the drug.
As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. The drug should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary. The drug should not be used as the first treatment for asthma.
For treatment of acute asthma attacks patients should be advised to have their short-acting bronchodilator available at all times.
Patients should be reminded to take the drug daily as prescribed even when asymptomatic.
Once asthma symptoms are controlled, consideration may be given to gradually reduce the dose of the drug. Regular review of patients as treatment is stepped down is important. The lowest effective dose of the drug should be used.
Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhaled than with oral corticosteroids. Possible systemic effects include: Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma.
Therefore, it is important that the patient is reviewed regularly, and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

DRUG INTERACTIONS
Beta-blockers (including eye drops) should be avoided in asthmatic patients. If beta-blockers are administered for compelling reasons, the effect of formoterol will be reduced or abolished.
On the other hand, concomitant use of other beta-adrenergic drugs can have potentially additive effects, therefore caution is required when theophylline or other beta-adrenergic drugs are prescribed concomitantly with formoterol.
Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines, monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.
In addition L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta$_2$-sympathomimetics.
Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.
There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.
Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of beta$_2$-agonists. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.
The drug contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

FERTILITY, PREGNANCY AND LACTATION
There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy or lactation. However studies of the effect of HFA-134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects.
Pregnancy
There are no relevant clinical data on the use of the drug in pregnant women. Animal studies using beclometasone dipropionate and formoterol combination showed evidence of toxicity to reproduction after high systemic exposure. Because of the tocolytic actions of beta$_2$-sympathomimetic agents particular care should be exercised in the run up to delivery. Formoterol should not be recommended for use during pregnancy and particularly at the end of pregnancy or during labour unless there is no other (safer) established alternative.
The drug should only be used during pregnancy if the expected benefits outweigh the potential risks.
Lactation
There are no relevant clinical data on the use of the drug in lactation in humans.
Although no data from animal experiments are available, it is reasonable to assume that beclometasone dipropionate is secreted in milk, like other corticosteroids.
While it is not known whether formoterol passes into human breast milk, it has been detected in the milk of lactating animals.
Administration of the drug to women who are breast-feeding should only be considered if the expected benefits outweigh the potential risks.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
The drug is unlikely to have any effect on the ability to drive and operate machinery.

ADVERSE REACTIONS
As the drug contains beclometasone dipropionate and formoterol fumarate dihydrate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.
Undesirable effects which have been associated with beclometasone dipropionate and formoterol administered as a fixed

combination and as single agents are given below, listed by system organ class. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (≤1/10,000). Common and uncommon ADRs were derived from clinical trials in asthmatic and COPD patients.
Infections and infestations: Common: Pharyngitis, oral candidiasis; Uncommon: Influenza, oral fungal infection, oropharyngeal and oesophageal candidiasis, vulvovaginal candidiasis, gastroenteritis, sinusitis, rhinitis, pneuomonia*
Blood and lymphatic system disorders: Uncommon: Granulocytopenia; Very Rare: Thrombocytopenia
Immune system disorders: Uncommon: Allergic dermatitis; Very Rare: Hypersensitivity reactions including erythema, lips, face, eye and pharyngeal oedema
Endocrine disorders: Very Rare: Adrenal suppression
Metabolism and nutrition disorders: Uncommon: Hypokalemia and hyperglycemia
Psychiatric disorders: Uncommon: Restlessness; Unknown:Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)
Nervous system disorders: Common: Headache; Uncommon: Tremor, dizziness
Eye disorders: Very rare: Glaucoma, cataract
Ear and labyrinth disorders: Uncommon: Otosalpingitis
Cardiac disorders: Uncommon: Palpitations, electrocardiogram QT corrected interval prolonged, electrocardiogram change, tachycardia, tachyarrhythmia, atrial fibrillation*; Rare: Ventricular extrasystoles, angina pectoris
Vascular disorders: Uncommon: Hyperaemia, flushing
Respiratory, thoracic and mediastinal disorders: Common: Dysphonia; Uncommon: Rhinitis, cough, productive cough, throat irritation, asthmatic crisis; Rare: Paradoxical bronchospasm; Very Rare: Dyspnea, exacerbation of asthma
Gastrointestinal disorders: Uncommon: Diarrhea, dry mouth, dyspepsia, dysphagia, burning sensation of the lips, nausea, dysgeusia
Skin and subcutaneous tissue disorders: Uncommon: Pruritus, rash, hyperhidrosis, urticaria; Rare: Angioedema
Musculoskeletal, connective tissue and bone disorders: Uncommon: Muscle spasms, myalgia; Very Rare: Growth retardation in children and adolescents
Renal and urinary disorders: Rare: Nephritis
General disorders and administration site conditions: Very Rare: Peripheral oedema
Investigations: Uncommon: C-reactive protein increased, platelet count increased, free fatty acids increased, blood insulin increased, blood ketone body increased, blood cortisol decrease*; Rare: Blood pressure increased, blood pressure decreased; Very Rare: Bone density decreased
* One related non serious case of pneumonia was reported by one patient treated with the drug in a pivotal clinical trial in COPD patients. Other adverse reactions observed in COPD clinical trials were: reduction of blood cortisol and atrial fibrillation.
As with other inhalation therapy, paradoxical bronchospasm may occur (Special Warnings and Precautions for Use).
Among the observed adverse reactions those typically associated with formoterol are:
Hypokalaemia, headache, tremor, palpitations, cough, muscle spasms and prolongation of QTc interval.
Adverse reactions typically associated with the administration of beclometasone dipropionate are: oral fungal infections, oral candidiasis, dysphonia, throat irritation.
Dysphonia and candidiasis may be relieved by gargling or rinsing the mouth with water or brushing the teeth after using the product. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst continuing the treatment with the drug.
Systemic effects of inhaled corticosteroids (e.g. beclometasone dipropionate) may occur particularly when administered at high doses or prescribed for prolonged periods. These may include adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma.
Hypersensitivity reactions including rash, urticaria, pruritus and erythema, and oedema of the eyes, face, lips and throat may also occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

OVERDOSAGE

Inhaled doses of the drug up to twelve cumulative actuations (total beclometasone dipropionate 1200 micrograms, formoterol 72 micrograms) have been studied in asthmatic patients. The cumulative treatments did not cause abnormal effect on vital signs and neither serious nor severe adverse events were observed.
Excessive doses of formoterol may lead to effects that are typical of beta$_2$-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalaemia and hyperglycaemia.
In case of overdose of formoterol, supportive and symptomatic treatment is indicated. Serious cases should be hospitalized. Use of cardioselective beta-adrenergic blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm. Serum potassium should be monitored.
Acute inhalation of beclometasone dipropionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function recovers in a few days, as verified by plasma cortisol measurements. In these patients, treatment should be continued at a dose sufficient to control asthma.
Chronic overdose of inhaled beclometasone dipropionate: risk of adrenal suppression. Monitoring of adrenal reserve may be necessary. Treatment should be continued at a dose sufficient to control asthma.

DOSAGE AND ADMINISTRATION

The drug is for inhalation use.

ASTHMA

It is not intended for the initial management of asthma. The dosage of the components of the drug is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of beta$_2$-agonists and/or corticosteroids by individual inhalers should be prescribed.
There are 2 treatment approaches:
A. Maintenance Therapy: Beclometasone dipropionate/Formoterol fumarate dihydrate (Foster) is taken as regular maintenance treatment and patients are advised to have their separate "as needed" rapid-acting bronchodilator available for rescue use at all times.
Dose recommendations for adults 18 years and above: One or two inhalations twice daily.
The maximum daily dose is 4 inhalations
B. Maintenance and Reliever Therapy: Beclometasone dipropionate/Formoterol fumarate dihydrate (Foster) is taken as a regular maintenance treatment and as needed in response to asthma symptoms. Patients are advised to always have Beclometasone dipropionate/Formoterol fumarate dihydrate (Foster) available for rescue use.
Beclometasone dipropionate/Formoterol fumarate dihydrate (Foster) maintenance and reliever therapy should especially be considered for patients with:
- not fully controlled asthma and in need of reliever medication
- asthma exacerbations in the past requiring medical intervention

Dose recommendations for adults 18 years and above: The recommended maintenance dose is 1 inhalation twice daily (one inhalation in the morning and one inhalation in the evening). Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken.
The maximum dose is 8 inhalations.
Patients requiring frequent use of rescue inhalations daily should be strongly recommended to seek medical advice. Their asthma should be reassessed and their maintenance therapy should be reconsidered.

Dose recommendations for children and adolescents under 18 years:
The safety and efficacy of Beclometasone dipropionate/Formoterol fumarate dihydrate (Foster) in children and adolescents under 18 years of age have not been established yet. No data are available with the drug in children under 12 years of age. Therefore the drug is not recommended for children and adolescents under 18 years until further data become available.
Patients should be regularly reassessed by a doctor, so that the dosage of Beclometasone dipropionate/Formoterol fumarate dihydrate (Foster) remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.
Patients should be advised to take Beclometasone dipropionate/Formoterol fumarate dihydrate (Foster) every day even when asymptomatic.

COPD

Dose recommendations for adults 18 years and above: Two inhalations twice daily.

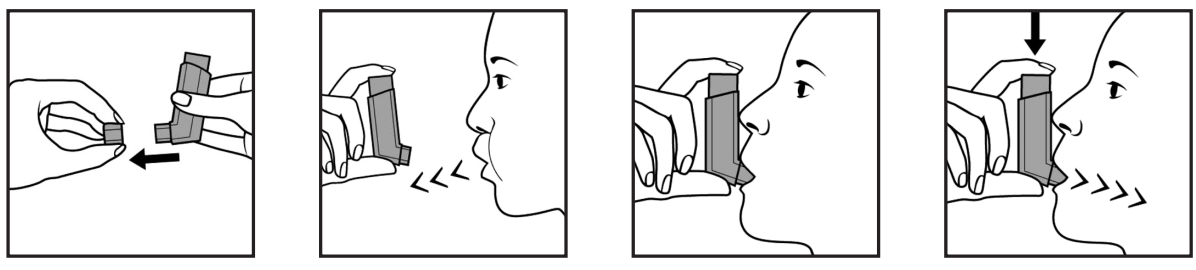
Special patient groups:

There is no need to adjust the dose in elderly patients. There are no data available for use of Beclometasone dipropionate/Formoterol fumarate dihydrate (Foster)in patients with hepatic or renal impairment.

Method of Administration:

To ensure proper administration of the drug, the patient should be shown how to use the inhaler correctly by a physician or other health professional. Correct use of the pressurized metered dose inhaler is essential in order that treatment is successful.
The patient should be advised to read the package insert carefully and follow the instructions for use as given in the insert.
Before using the inhaler for the first time or if the inhaler has not been used for 14 days or more, one actuation should be released into the air in order to ensure that the inhaler is working properly.
Whenever possible patients should stand or sit in an upright position when inhaling from their inhaler.
The steps below should be followed:

1. Remove the protective cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt or any other foreign objects.
2. Breathe out as slowly and deeply as possible.
3. Hold the canister vertically with its body upwards and put the lips around the mouthpiece. Do not bite the mouthpiece
4. At the same time, breathe in slowly and deeply through the mouth. After starting to breathe in press down on the top of the inhaler to release one puff.



5. Hold the breath for as long as possible and, finally, remove the inhaler from the mouth and breathe out slowly. Do not breath out into the inhaler.

Should a further puff be needed, keep the inhaler in a vertical position for about half a minute and repeat steps 2 to 5.
After use, close with protective cap.
IMPORTANT: Do not perform steps 2 to 5 too quickly.
If mist appears following inhalation, either from the inhaler or from the sides of the mouth, the procedure should be repeated from step 2.
For patients with weak hands, it may be easier to hold the inhaler with both hands. Therefore the index fingers should be placed on the top of the inhaler canister and both thumbs on the base of the inhaler.
Patients should rinse their mouth or gargle with water or brush the teeth after inhaling.

Cleaning

For the regular cleaning of the inhaler, patients should remove the cap from the mouthpiece and wipe the outside and inside of the mouthpiece with a dry cloth. They should not use water or other liquids to clean the mouthpiece.
Patients who find it difficult to synchronise aerosol actuation with inspiration of breath, may use a spacer device. They should be advised by their doctor, pharmacist or a nurse in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs. This may be obtained by the patients using the spacer device by one continuous slow and deep breath through the spacer, without any delay between actuation and inhalation.

STORAGE

Shelf-life: 17 months
Prior to dispensing to the patient: Store in a refrigerator (2-8°C) (for a maximum of 15 months).
After dispensing: Store at temperatures not exceeding 30°C (for a maximum of 2 months).
The canister contains a pressurized liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY

Pressurized aluminium alloy canister with a metering valve fitted into a polypropylene plastic actuator and plastic protective cap (120 actuations) in individual box x 1's

Manufactured by :
CHIESI FARMACEUTICI S.p.A
Via Palermo, 26/A 43122 Parma, Italy
Imported by :
OEP PHILIPPINES, INC.
Rm 606 6/F SEDCCO I Bldg., cor. Rada & Legaspi Sts.,
Legaspi Village, Makati City
Distributed by :
Zuellig Pharma Corporation
Km 14 West Service Road, South Super Highway cor. Edison Ave.,
Brgy. Sun Valley, Parañaque City

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