PRODUCT MONOGRAPH

MYLAN-BECLO AQ.

Nasal Spray
(Beclomethasone Dipropionate Aqueous Suspension)

50 mcg/metered dose

Corticosteroid for nasal use

Mylan Pharmaceuticals ULC
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Control#: 129658

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Date of Revision:

PRODUCT MONOGRAPH

NAME OF DRUG

MYLAN-BECLO AQ
(Beclomethasone Dipropionate Aqueous Suspension)

50 mcg/metered dose

THERAPEUTIC CLASSIFICATION

Corticosteroid for nasal use

ACTIONS AND CLINICAL PHARMACOLOGY

Beclomethasone dipropionate is a potent anti-inflammatory steroid with a strong topical and weak systemic activity. When inhaled intranasally in therapeutic doses, it has a direct anti-inflammatory action within the nasal mucosa, the mechanism of which is not yet completely defined. The minute amount absorbed in therapeutic doses has not been shown to exert any apparent clinical systemic effects.

INDICATIONS AND CLINICAL USE

MYLAN-BECLO AQ (beclomethasone dipropionate aqueous suspension) is indicated for the treatment of perennial and seasonal allergic rhinitis unresponsive to conventional treatment.

CONTRAINDICATIONS

MYLAN-BECLO AQ (beclomethasone dipropionate aqueous suspension) is contraindicated for patients with active or quiescent tuberculosis or untreated fungal, bacterial and viral infections.

MYLAN-BECLO AQ is also contraindicated in patients with a history of hypersensitivity to any of its ingredients.

WARNINGS

In patients previously on high doses of systemic steroids, transfer to MYLAN-BECLO AQ (beclomethasone dipropionate aqueous suspension) may cause withdrawal symptoms such as tiredness, aches and pains and depression. In severe cases, adrenal insufficiency may occur, necessitating the temporary resumption of systemic steroids. Careful attention must be given to

patients with asthma and other clinical conditions in whom a rapid decrease in systemic steroid may cause a severe exacerbation of their symptoms.

The safety of MYLAN-BECLO AQ in pregnancy has not been established. If used, the expected benefits should be weighed against the potential hazard to the fetus, particularly during the first trimester of pregnancy. Like other glucocorticosteroids, beclomethasone dipropionate is teratogenic to rodent species (see under TOXICOLOGY). The relevance of these findings to humans has not yet been established. Infants born of mothers who have received substantial doses of glucocorticosteroids during pregnancy should be carefully observed for hypoadrenalism.

PRECAUTIONS

The replacement of a systemic steroid with MYLAN-BECLO AQ (beclomethasone dipropionate aqueous suspension) has to be gradual and carefully supervised by the physician. The guidelines under "Administration" should be followed in all such cases.

Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. During long-term therapy, pituitary-adrenal function and hematological status should be periodically assessed.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

During MYLAN-BECLO AQ therapy, the possibility of atrophic rhinitist, and/or pharyngeal candidiasis should be kept in mind.

With the use of usual doses of nasal beclomethasone, significant suppression of growth has not been strongly documented. If significant systemic absorption of nasal adrenocorticoids occurs, adrenal suppression and growth suppression may result in pediatric patients.

Use in Obstetrics:

Adrenocorticoids cross the placenta. Unnecessary administration of drugs during pregnancy is undesirable.

Patients with Special Diseases and Conditions:

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Drug Interactions:

Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Patients should be informed that the full effect of MYLAN-BECLO AQ therapy is not achieved until 2 to 3 days of treatment have been completed. Treatment of seasonal rhinitis should, if possible, start before the exposure to allergens.

Treatment with MYLAN-BECLO AQ should not be stopped abruptly but tapered off gradually. Because of the inhibitory effect of corticosteroids on wound healing, in patients who have had recent nasal surgery or trauma, a nasal corticosteroid should be used with caution until healing has occurred.

Children

MYLAN-BECLO AQ is not presently recommended for children younger than 6 years of age.

Lactation

Glucocorticosteroids are secreted in human milk. It is not known whether beclomethasone dipropionate would be secreted in human milk, but it is suspected to be likely. The use of MYLAN-BECLO AQ in nursing mothers requires that the possible benefits of the drug be weighed against the potential hazards to the infant.

ADVERSE REACTIONS

No major side-effects attributable to beclomethasone dipropionate aqueous suspension have been reported. In controlled clinical trials involving 269 patients the following adverse events and incidences thereof were observed:

sneezing	26%
stinging	24%
sore throat	10%
cough	8%
epistaxis	7%
headache	7%
dizziness	6%
nausea	6%
nasal drying/crusting	5%
lethargy	3%
stomach pains	3%

Rare instances of nasal mucosal ulceration and nasal septum perforation have been reported following intranasal application of aerosol and aqueous corticosteroids. Localized infections of the nose and pharynx with Candida albicans have occurred rarely (see PRECAUTIONS). Rare cases of raised intraocular pressure of glaucoma in association with intranasal formulations of beclomethasone dipropionate have been reported. Immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash and bronchospasm, have been reported rarely after the use of beclomethasone dipropionate oral or intranasal inhalers.

When patients are transferred to MYLAN-BECLO AQ from a systemic steroid, allergic conditions such as asthma or eczema may be unmasked.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Like any other nasally administered corticosteroid, acute overdosing is unlikely in view of the amount of active ingredient present. However, when used chronically in excessive doses (above 600 μg or 12 sprays per day of MYLAN-BECLO AQ or in conjunction with other corticosteroid formulations, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of MYLAN-BECLO AQ should be discontinued slowly consistent with accepted procedures for discontinuation of chronic steroid therapy (see DOSAGE AND ADMINISTRATION).

The restoration of hypothalamic-pituitary-axis may be slow; during periods of pronounced physical stress (i.e. severe infections, trauma, surgery) a supplement with systemic steroids may be advisable.

DOSAGE AND ADMINISTRATION

The usual dose for patients of all ages who received no previous systemic steroid is two applications (100 μg of beclomethasone dipropionate) into each nostril twice daily. Maximum daily dose should not exceed 12 applications (600 μg of beclomethasone dipropionate) in adults and 8 applications (400 μg of beclomethasone dipropionate) in children.

When MYLAN-BECLO AQ (beclomethasone dipropionate aqueous suspension) is used concurrently with other beclomethasone dipropionate inhalers, the combined total daily dose should not exceed the maximum daily recommended dose of beclomethasone dipropionate.

The safety and efficacy of MYLAN-BECLO AQ in children under 6 years of age has not been established.

Since the effect of MYLAN-BECLO AQ depends on its regular use, patients must be instructed to take the nasal inhalations at regular intervals and not as with other nasal sprays, as they feel necessary. They should also be instructed in the correct method, which is to blow the nose, then insert the nozzle firmly into the nostril, compress the opposite nostril and actuate the spray while inspiring through the nose, with the mouth closed.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of action. In such cases it is advisable to use a nasal vasoconstrictor for two to three days prior to MYLAN-BECLO AQ Careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids when transferred to MYLAN-BECLO AQ. Initially, MYLAN-BECLO AQ and the systemic corticosteroid must be given concomitantly, while the dose of the latter is gradually decreased. The usual rate of withdrawal of the systemic steroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close supervision. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 2.5 mg of prednisone (or equivalent) every ten days. If withdrawal symptoms appear, the

previous dose of the systemic steroid should be resumed for a week before further decrease is attempted.

An improvement of symptoms usually becomes apparent within a few days after the start of therapy. However, symptomatic relief may not occur in some patients for as long as two weeks. MYLAN-BECLO AQ should not be continued beyond three weeks in the absence of significant symptomatic improvement.

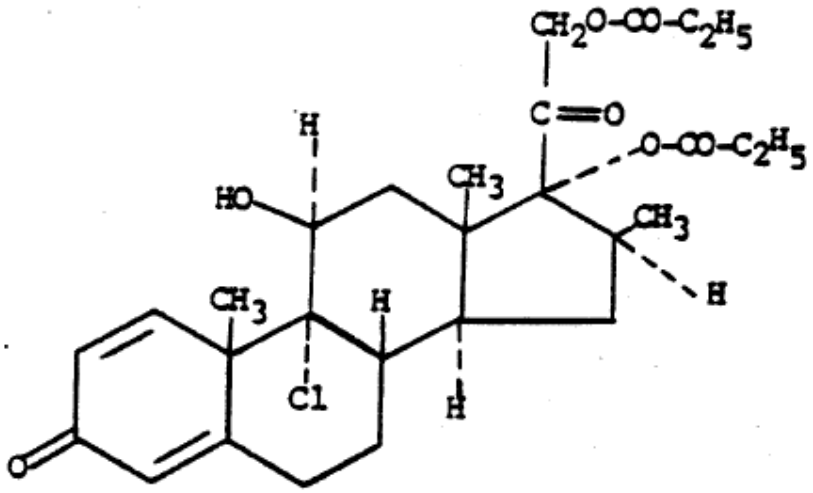
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Beclomethasone Dipropionate

Chemical Name: 9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4diene-3,20-dione-17,21-dipropionate

Structural Formula:



Beclomethasone Dipropionate

Molecular Formula: $C_{28}H_{37}C10_7$

Molecular Weight: 521

Description: Beclomethasone dipropionate is an odourless, white-to-creamy-white powder. It is very slightly soluble in water, very soluble in chloroform, and freely soluble in acetone and alcohol. It has a melting point of about 212°C.

Composition:

MYLAN-BECLO AQ (beclomethasone dipropionate aqueous suspension) is a metered dose nasal spray which contains beclomethasone dipropionate, benzalkonium chloride, purified water, dextrose,

microcrystalline cellulose, phenyl ethanol, polysorbate and sodium carboxymethyl cellulose. Each spray delivers 50 mcg of beclomethasone dipropionate.

Stability and Storage Conditions:

Store between 15°C and 30°C. Protect from light. Do not refrigerate.

AVAILABILITY OF DOSAGE FORMS

MYLAN-BECLO AQ (beclomethasone dipropionate aqueous suspension) is a suspension of beclomethasone dipropionate in an amber glass bottle fitted with a metering pump and a nasal applicator. Each spray delivered by the nasal applicator contains 50 μg of beclomethasone dipropionate. There are 200 doses in each bottle.

INFORMATION FOR THE PATIENT

MYLAN-BECLO AQ

Nasal Spray

(Beclomethasone Dipropionate Aqueous Suspension)

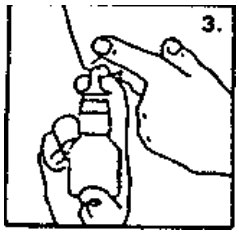
50 µg/metered dose

Before using your MYLAN-BECLO AQ Nasal Spray, please read this leaflet carefully and follow these instructions.

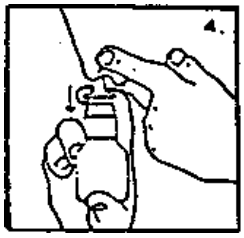
Directions for use

1. Remove the dust cap and lock ring from the nasal applicator.
Shake the bottle.

2. The very first time the spray is used, prime the pump by pressing downwards on the white collar using your index and middle fingers while supporting the base of the bottle with your thumb. Press down until a fine spray appears. The spray is now ready for use. It should be necessary to prime the pump only when using the spray for the first time.



3. Gently blow your nose. Close one nostril. Tilt your head forward slightly and, keeping the bottle upright, carefully insert the nasal applicator into the other nostril.



4. For each spray your physician has instructed you to take, press firmly downwards once on the white collar using your index and middle fingers while supporting the base of the bottle with your thumb. Breathe gently inwards

through the nostril, then breathe out through the mouth.

5. Repeat the procedure for your other nostril.
6. Replace the lock ring and the dust cap.

Dosage

It is essential that you use MYLAN-BECLO AQ nasal spray regularly at the intervals recommended by your doctor. Do not stop or change dosage without consulting your doctor. Children should use MYLAN-BECLO AQ nasal spray under the supervision of an adult who is aware of proper use.

The usual dose for patients of all ages who received no previous systemic steroid is two applications (100 μg of beclomethasone dipropionate) into each nostril twice daily. Maximum daily dose should not exceed 12 applications (600 micrograms of beclomethasone dipropionate) in adults and 8 applications (400 micrograms of beclomethasone dipropionate) in children. MYLAN-BECLO AQ nasal spray should not be used in children under six years of age.

After taking your medicine

Contact your doctor if:

- you do not detect any improvement in 3 weeks
- nasal irritation occurs
- coloured (yellow or green) nasal secretions appear
- repeated nasal bleeding occurs
-

Caution

MYLAN-BECLO AQ nasal spray is not intended to give instant relief of your nasal congestion but to correct the underlying disorder responsible for your symptoms. It may take a few days (and up to 2 weeks) before you notice any improvement.

Cleaning

To clean the nasal applicator, remove the white dust cap and the lock ring, press gently upwards on the white collar and the nasal applicator will come free. Wash the applicator and dust cap under cold water. Dry and replace the applicator with the dust cap and lock ring back in position.
If the nasal applicator becomes blocked, remove the dust cap, pull off the complete pump mechanism and soak it in warm water for a few minutes. Rinse with cold water, dry and refit to bottle.
Discard three months after first using the spray.

PHARMACOLOGY

Metabolism: Two tritium-labelled beclomethasone dipropionate preparations, one labelled on the 16 position, the other labelled on the C_{21} propionate group, were used to study the in vitro metabolism of the drug by human lung slices and rat lung homogenate. In both cases the drug was metabolized rapidly into beclomethasone-17mono-propionate and more slowly into beclomethasone.

Rats were exposed in a chamber to 19 x 50 μg bursts of beclomethasone dipropionate over a five-minute period. The highest concentration of radioactivity was present in the nose and mouth. Two hours after inhalation, the tissue radioactivity was reduced by about 80%. The lung concentration was 140-420 μg/g. Extrapolation to therapeutic human conditions shows that the total exposure of rats represented twelve times the single human dose.

Excretion: Following oral administration of 4-10 mg/kg of radioactive beclomethasone dipropionate to rats, 50-90% was excreted in the feces and 1.54.4% in the urine after forty-eight hours. In the feces, 65% of the drug was present unchanged, and small amounts of beclomethasone propionate and beclomethasone were found. In the urine, each metabolite was present in small quantities. In man, the major metabolites are the same as in rats. After oral dosage, 10-15% of the radioactivity was found in the urine and 35-65% in the feces.

Glucocorticoid Effect: Thymolytic tests in mice treated orally or subcutaneously showed results similar to those with betamethasone. In rats, the thymolytic effect of beclomethasone dipropionate is very weak.

Glycogen deposition test in mice showed an activity 1/10 that of dexamethasone. In rats, the drug caused no glycogen deposition. Pituitary-adrenal suppression test, in mice, showed an activity three times stronger than that of betamethasone, when 40 μg/kg of beclomethasone dipropionate was given subcutaneously. In rats, however, only a large dose of 100 mg/kg showed any suggestion of pituitary suppression.

Mineralocorticold activity was minimal as shown in electrolyte changes after administration of 100 or 1000 μg/kg of beclomethasone dipropionate to adrenalectomized rats.

Anti-inflammatory activity was assessed by the carrageenin and formalin induced edema and inhibition of cotton-pellet granuloma. In all tests, the activity of beclomethasone dipropionate was 9-40 times higher than that of hydrocortisone.

In conclusion, beclomethasone dipropionate is a potent anti-inflammatory steroid both in the rat and the mouse. However, in the mouse, the drug behaves as a potent glucocorticoid, while in the rat it is virtually devoid of typical glucocorticoid effects.

Human Pharmacoloay: Inhalation of beclomethasone dipropionate 1 to 4 mg/day for four weeks, showed that the daily dose of 1 mg causes no significant adrenal suppression. At 2 mg/kg, the results are equivocal and at 4 mg, there is clear evidence of adrenal suppression.

Studies in five volunteers over a four-week period showed that the addition of a daily dose of 1 mg per day beclomethasone dipropionate intranasally to that of 1 mg/day beclomethasone dipropionate intrabronchially, does not lead to adrenal suppression.

Clinical Trials: A double-blind, double-placebo comparative study of beclomethasone dipropionate (BDP) aqueous nasal spray and the conventional BDP pressurized aerosol spray was conducted in 373 patients with seasonal rhinitis, including 51 children 12 years of age or less. The dosage regimen for both preparations was 2 applications (100 μg) into each nostril twice daily (i.e., 400 μg /day). After two weeks of treatment there were no statistically significant differences between the two treatment groups with regard to symptom scores or concurrent consumption of antihistamine tablets. In the physicians' assessments the two BDP preparations were equally effective in reducing and controlling nasal symptoms with 72% of patients in each group demonstrating a "good" or "very good" response to

treatment. A total of 224 complaints of putative adverse effects, equally divided between the two treatment groups, were elicited during the study.

In another study, forty-two subjects took part in a double-blind, double-dummy, paralleled group study to compare the efficacy and tolerance of a nasal spray containing an aqueous suspension of beclomethasone dipropionate with the conventional pressurized spray in controlling the symptoms of seasonal rhinitis. Each patient received 100 μg beclomethasone dipropionate into each nostril twice daily for 14 days. Evaluation of daily symptom scores, and the physician's and subject's assessment of treatment, demonstrated that both sprays were equally effective in alleviating symptoms, with similar low incidence of side-effects. The aqueous spray may be considered an effective alternative treatment in the management of seasonal rhinitis.

TOXICOLOGY

ANIMAL

Acute Toxicity: Oral LD_{50} in mice: above 3 g/kg; in rats: above 1 g/kg. Guinea pigs, rabbits, cats and dogs survived single oral doses of 60 mg of beclomethasone dipropionate. This dose caused bloody diarrhea and inflammation of the intestinal tract.

Subacute Toxicity in rats: Daily doses from 0.9 to 100 mg/kg were given subcutaneously for one week, and 0.02 to 3.0 mg/kg for four weeks. No animal died. High doses diminished growth, serum protein and inorganic phosphate. There was some elevation of SGPT. Two rats had chronic inflammatory changes in the bronchi.
In dogs, daily intramuscular injection of beclomethasone dipropionate ranging from 0.5 mg/kg to 4.5 mg/kg for four weeks caused decreased leukocyte count, and typical glucocorticoid type organ changes.

Chronic Toxicity in rats: Subcutaneous injection of beclomethasone dipropionate at daily doses from 0.1 mg/kg to 300 mg/kg for three to six months duration, gave the following results: decreased food

consumption and body weight, reduction of leukocytes and lymphocytes, increased SGPT, SGOT and alkaline phosphatase, fat and glycogen deposition in the liver. The sites of injection showed hardening and irritation in the high-dose groups. There was no spontaneous mortality.

Local effect on the lungs after inhalation: One hundred and fifty rats were exposed intermittently to beclomethasone dipropionate aerosol for twenty-six weeks at estimated dosages of ten, twenty and forty times the human dose. In addition, in the last thirteen weeks, some rats received daily oral doses of beclomethasone dipropionate at ten, thirty and one hundred times the human therapeutic level, to account for any gross swallowing of the drug during inhalation. No gross pathological changes attributable to medication were seen. Histologically, most animals had minimal perivascular and peribronchial accumulations of lymphocytes. Some animals had signs of chronic respiratory disease which is commonly seen in laboratory rats.
Dogs were exposed to 50 μg and 100 μg of beclomethasone dipropionate per burst for three months, representing approximately two hundred and fifty times the human exposure. There were no changes in the respiratory tract attributable to the medication.

HUMAN
Nasal biopsies from patients treated with intranasal beclomethasone dipropionate aerosol for six weeks showed no drug-related abnormalities.

Beclomethasone dipropionate aqueous nasal spray was administered to forty healthy volunteers who were asked to assess the local irritancy of the preparation. None of the subjects judged the spray to be sufficiently irritating so as to possibly compromise treatment.

TERATOGENIC TESTS
In mice, treated from the first day to the eighteenth day of pregnancy with beclomethasone dipropionate 3 mg/kg/day subcutaneously, there was an increased number of resorption sites, reduced number of live fetuses and reduced weight of live-born litters. There was an increased incidence of cleft palates and retarded maturation of the sternum. These results were similar to those obtained with hydrocortisone at a corresponding dose (60 mg/kg/day).

In rabbits, treated with beclomethasone dipropionate from the first to the thirteenth day of pregnancy at the dose of 0.1 mg/kg/day, there was a complete resorption of fetuses. At the dose of 0.01 mg/kg/day, there was no toxicity to pregnant animals, while there was some cleft palate formation in the offsprings. At the dose of 0.005 mg/kg/day, there was no teratogenic effect.

Studies in rats, mice and rabbits have shown that subcutaneously administered beclomethasone causes increased fetal resorptions and birth defects.

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