SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MONALIZ 0.05% Nasal Spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation contains
Active substance:
Mometasone furoate (monohydrate)…….50 mcg

Each actuation contains 51.75 mcg mometasone furoate monohydrate equal to 50 mcg mometasone furoate.

Excipients:
Benzalkonium chloride……0.2 mg/g
For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Nasal suspension used with a metered spray pump.
White, opaque suspension, homogenous when shaken.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MONALIZ is indicated for the treatment of the symptoms of seasonal or perennial allergic rhinitis, in adults, adolescents and children 6 to 11 years of age.

MONALIZ is indicated for the prophylaxis of seasonal allergic rhinitis in adults and children 12 years of age and older.

MONALIZ can be used in children 2 to 6 years of age diagnosed with allergic rhinitis.

Prophylactic treatment should be initiated 2 to 4 weeks prior to the anticipated start of pollen season.

MONALIZ is used in the treatment of chronic rhinosinusitis with or without nasal polyps in adults and acute rhinosinusitis in children aged 12 years and over and in adults (in addition to antibiotics in bacterial rhinosinusitis).

MONALIZ is used also for the treatment of nasal polyps and relevant symptoms including congestion and loss of sense of smell in adults 18 years of age and older.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Prior to first administration or if the spray pump has not been used for 14 days or longer, to re-prime the spray pump, shake container well and actuate the pump 10 times. Each actuation delivers 100 mg of mometasone furoate suspension containing mometasone furoate monohydrate equivalent

to 50 mcg mometasone furoate. If the pump is not used for 14 days or longer, re-prime the pump with 2 actuations until a uniform spray is observed, before next use.

Seasonal allergic or perennial rhinitis:
For adults (including elderly) and adolescents:
The usual recommended daily dose for prophylaxis and treatment is 2 actuations (50 mcg/actuation) in each nostril once daily giving a total dose of 200 mcg. Once symptoms are controlled, dose reduction to 1 actuation in each nostril giving a total dose of 100 mcg may be effective for maintenance.

Seasonal allergic or perennial rhinitis:
Adults (including elderly patients) and adolescents: The generally recommended daily dose for prophylaxis and treatment is 200 micrograms (50 micrograms/1 spray) administered twice daily in each nostril. Once symptoms are controlled, the maintenance dose can be reduced to 100 micrograms (one spray in each nostril) administered once daily.

If symptoms are inadequately controlled, the dose may be increased to a maximum daily dose of 4 actuations in each nostril once daily giving a total dose of 400 mcg.

Dose reduction is recommended following control of symptoms.

Children between the ages of 2 and 11 years:
The recommended daily dose is 1 actuation in each nostril once daily (50 mcg/ 1 actuation) giving a total dose of 100 mcg.

Mometasone furoate demonstrated a clinically significant onset of action 12 hours after the first dose in some patients with allergic rhinitis. However, full benefit of treatment may not be achieved in the first 48 hours. Therefore, the patient should continue regular use to achieve full therapeutic benefit.

Treatment of nasal polyposis:
In adults (including older patients) and adolescents aged 18 years and older:
The recommended daily dose is 2 actuations (50 mcg/ 1 actuation) in each nostril once daily giving a total dose of 200 mcg. If after 5 to 6 weeks symptoms are inadequately controlled, the dose may be increased to a daily dose of 2 sprays in each nostril twice daily giving a total dose of 400 mcg. If no improvement in symptoms is seen after 5 to 6 weeks of twice daily administration, alternative therapies should be considered.

Efficacy and safety studies of mometasone furoate for the treatment of nasal polyposis were 4 months in duration.

Rhinosinusitis Treatment:
The recommended daily dose for children 12 years of age and older and adults is 200 micrograms (50 micrograms/1 spray) administered twice daily in each nostril. If symptoms are not adequately controlled, the daily dose may be increased to a total of 400 micrograms, 2 sprays into each nostril twice daily.

Method of administration
MONALIZ is used by spraying into the nostrils.

Before applying the first dose, shake the pump well and spray 10 times until the medicine appears to be spraying evenly. If the pump is not used for 14 days or longer, re-prime the pump with 2 actuations until a uniform spray is observed, before next use. Shake container well before each use. The bottle should be discarded after the labeled number of actuations or within 2 months of first use.

Additional information for special populations
Renal/Hepatic insufficiency
There is no data for patients with renal and hepatic insufficiency.

Pediatric population
MONALIZ is not recommended for infants and young children unless absolutely necessary.

Systemic effects of nasal corticosteroids may be seen, particularly at prolonged use of high doses. Growth retardation has been reported in children receiving nasal corticosteroids at authorized therapeutic doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is maintained. In addition, consideration should be given to referring the patient to a pediatric specialist.

Geriatric population
Treatment of nasal polyposis in geriatric population is the same with that in adults.

4.3 Contraindications
MONALIZ should not be used in case of hypersensitivity to any of its ingredients.
MONALIZ should not be used in the presence of untreated localized infections involving the nasal mucosa.
Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal surgery or trauma should not use a nasal corticosteroid until healing has occurred.

4.4 Special warnings and precautions for use
MONALIZ should be used with caution, if at all, in patients with active or latent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections or ocular herpes simplex.

Following 12 months of treatment with mometasone furoate, there was no evidence of atrophy of the nasal mucosa; also, mometasone furoate tended to reverse the nasal mucosa closer to a normal histologic phenotype. As with any long-term treatment, patients using MONALIZ over several months or longer should be examined periodically for possible changes in the nasal mucosa. If localized fungal infection of the nose or pharynx develops, discontinuance of MONALIZ therapy or appropriate treatment may be required. Persistence of nasopharyngeal irritation may be an indication for discontinuing MONALIZ.

Although MONALIZ will control the nasal symptoms in most patients, the concomitant use of appropriate additional therapy may provide additional relief of other symptoms (particularly ocular symptoms).

There is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with MONALIZ. However, patients who are transferred from long-term

administration of systemically active corticosteroids to MONALIZ require careful attention. Systemic corticosteroid withdrawal in such patients may result in adrenal insufficiency for a number of months until recovery of HPA axis function. If these patients exhibit signs and symptoms of adrenal insufficiency, systemic corticosteroid administration should be resumed and other modes of therapy and appropriate measures instituted.

During transfer from systemic corticosteroids to MONALIZ some patients may experience symptoms of withdrawal from systemically active corticosteroids (e.g., joint and/or muscular pain, lassitude, and depression initially) despite relief from nasal symptoms. They should be encouraged to continue MONALIZ therapy. Such transfer may also unmask pre-existing allergic conditions, such as allergic conjunctivitis and eczema, previously suppressed by systemic corticosteroid therapy.

The safety and efficacy of mometasone furoate has not been studied for use in the treatment of unilateral polyps, polyps associated with cystic fibrosis, or polyps that completely obstruct the nasal cavities.

Unilateral polyps that are unusual or irregular in appearance, especially if ulcerating or bleeding, should be further evaluated.

Patients receiving corticosteroids who are potentially immune-suppressed should be warned of the risk of exposure to certain infections (e.g., chickenpox, measles) and of the importance of obtaining medical advice if such exposure occurs.

Following the use of intranasal corticosteroids, instances of nasal septum perforation or increased intraocular pressure have been reported very rarely.

Safety and efficacy of mometasone furoate for the treatment of nasal polyposis in children and adolescents under 18 years of age have not been studied.

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety (state of worry and fear), depression or aggression (particularly in children).

It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is maintained. In addition, consideration should be given to referring the patient to a pediatric specialist.

Treatment with higher than recommended doses may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Excipients:
MONALIZ contains benzalkonium chloride equivalent to 0.2 mg per g. Long-term use may cause

edema of the nasal mucosa.

4.5 Interaction with other medicinal products and other forms of interaction

A clinical interaction study of mometasone furoate with loratadine has been conducted. In these studies, mometasone furoate plasma concentrations were undetectable by sensitive assays with a lower limit of quantification of 50 pg/mL.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category is C.

Women of child-bearing potential/Birth Control (Contraception)
There are no adequate data as to its use in women of childbearing potential.

Pregnancy
There are insufficient data on the use of MONALIZ in pregnant women. Animal studies are insufficient with regard to the effects on pregnancy and embryonal development (see section 5.3). The potential risk for humans is unknown.

No adequate and controlled studies have been conducted in pregnant women. As with other nasal corticosteroid preparations, when deciding to use MONALIZ in pregnant women, the potential hazards to the mother, fetus, and infant should be weighed against the anticipated benefits. Infants born to mothers treated with corticosteroids during pregnancy should be carefully monitored for hypoadrenalism.

Breast-feeding
As with other nasal corticosteroid preparations, potential harm to the mother and baby should be weighed against the expected benefits when deciding on the use of MONALIZ in lactating women.

Reproductive Ability/Fertility
There are no clinical data concerning the effect of mometasone furoate on fertility.

4.7 Effects on ability to drive and use machines

The effect on the ability to drive and use machines is unknown.

4.8 Undesirable effects

Very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

Respiratory, thoracic and mediastinal disorders
Common: Epistaxis, pharyngitis, nasal burning, nasal irritation, nasal ulceration

Musculoskeletal, connective tissue and bone disorders,
Not known: Growth retardation in children upon use for prolonged periods

It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored.

General disorders and administration site conditions
Common: Headache

Epistaxis was generally self-limiting and mild in severity. It has occurred at a higher incidence compared to placebo (5%), but at a comparable or lower incidence when compared to the active control nasal corticosteroids studied (up to 15%). The incidence of all other effects was comparable with that of placebo.

In the pediatric population, the incidence of adverse events, e.g., headache (3%), epistaxis (6%), nasal irritation (2%) and sneezing (2%) was comparable to placebo.

- Nasal Polyposis: In patients treated for nasal polyposis, the overall incidence of adverse events was comparable to placebo and similar to that observed for patients with allergic rhinitis. Treatment-related adverse events reported in ≥1% of patients in clinical studies for polyposis are shown below:

Respiratory, thoracic and mediastinal disorders
Very common: Epistaxis with 200 mcg twice daily
Common: Upper respiratory tract infection with 200 mcg once daily, epistaxis with 200 mcg once daily
Uncommon: Upper respiratory tract infection with 200 mcg twice daily

Gastrointestinal disorders
Common: Throat irritation with 200 mcg twice daily

General disorders and administration site conditions
Common: Headache with 200 mcg once daily and 200 mcg twice daily

Rarely, immediate hypersensitivity reactions (including bronchospasm and dyspnea) may occur after intranasal administration of mometasone furoate monohydrate. Very rarely, anaphylaxis and angioedema have been reported.

Disturbances of taste and smell have been reported very rarely.

Following the use of intranasal corticosteroids, rare cases of nasal septum perforation or increased intraocular pressure and/or cataract have been reported.

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9 Overdose

Because the systemic bioavailability of mometasone furoate (using sensitive assay with a lower quantification limit such as of 0.25 pg/ml), is <1%, MONALIZ overdose is unlikely to require any precaution other than observation of the patient, followed by initiation of the appropriate prescribed

dosage. Inhalation or oral administration of excessive doses of corticosteroids may lead to suppression of HPA axis function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use-Corticosteroids
ATC code: R01AD09

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active.

It is likely that much of the mechanism for the anti-allergic and anti-inflammatory effects of mometasone furoate lies in its ability to inhibit the release of mediators of allergic reactions. Mometasone furoate significantly inhibits the release of leukotrienes from leucocytes of allergic patients.

In cell culture, mometasone furoate demonstrated high potency in inhibition of synthesis and release of IL-1, IL-5, IL-6 and TNFα; it is also a potent inhibitor of leukotriene production. In addition, it is an extremely potent inhibitor of the production of the Th2 cytokines, IL-4 and IL-5, from human CD4+ T-cells.

In studies utilizing nasal antigen challenge, mometasone furoate has shown anti-inflammatory activity in both the early- and late- phase allergic responses. This has been demonstrated by decreases (vs placebo) in histamine and eosinophil activity and reductions (vs. baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins.

In 28% of the patients with seasonal allergic rhinitis, mometasone furoate demonstrated a clinically significant onset of action within 12 hours after the first dose. The median (50%) onset time of relief is 35.9 hours.

In two studies in 1954 patients, mometasone furoate 200 micrograms twice daily was effective in significantly improving rhinosinusitis symptoms compared to placebo over the 15-day treatment period (P02683, $p<0.001$; P02692, $p=0.038$). In this study, assessment was based on the Major Symptom Score (MSS) composite of symptoms (facial pain/pressure/tenderness, sinus headache, rhinorrhea, postnasal drip, and nasal congestion/fullness). The amoxicillin 500 mg three times daily arm did not differ significantly from placebo in symptom reduction as assessed by MSS. SNOT-20 HRQL improved significantly with mometasone furoate at doses of 200 micrograms twice daily compared to placebo ($p=0.047$). Furthermore, during the post-treatment follow-up period, the number of relapses with mometasone furoate was low and comparable to the amoxicillin and placebo groups. Treatment beyond 15 days in acute rhinosinusitis has not been studied.

In a placebo-controlled clinical trial in which pediatric patients (n=49/group) were administered mometasone furoate 100 mcg daily for one year, no reduction in growth velocity was observed.

There are limited data available on the safety and efficacy of mometasone furoate in the pediatric population aged below 2 years and an appropriate dosage range cannot be established. In a study involving 48 children aged 3 to 5 years treated with intranasal mometasone furoate 50, 100 or 200 mcg/day for 14 days, there was no significant differences from placebo in the mean change in

plasma cortisol level in response to the tetracosactrin stimulation test.

5.2 Pharmacokinetic properties

General properties

Absorption:
Mometasone furoate, administered via nasal route, has a systemic bioavailability of <1% in plasma, using a sensitive assay with a lower quantification limit such as of 0.25 pg/ml. Mometasone furoate suspension is very poorly absorbed from the gastrointestinal tract.

Distribution:
It is not relevant as it is administered nasally.

Biotransformation:
The small amount that may be absorbed after swallowed accidentally undergoes extensive first-pass hepatic metabolism.

Elimination:
It is excreted in urine and bile.

Linearity/Non-Linearity:
No data available.

5.3 Preclinical safety data

Preclinical studies demonstrate that mometasone furoate is devoid of androgenic, antiandrogenic, estrogenic or antiestrogenic activity but, like other glucocorticoids, it exhibits some antiuterotrophic activity and delays vaginal opening in animal models at high oral doses of 56 mg/kg/day and 280 mg/kg/day.

Like other glucocorticoids, mometasone furoate showed a clastogenic potential *in-vitro* at high concentrations. However, no mutagenic effects can be expected at therapeutically relevant doses.

At a dose of 15 micrograms/kg, prolonged gestation, prolonged and difficult delivery, and decreased number of surviving offspring, body weight, and weight gain occurred. There was no effect on fertility.

Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Teratology studies were conducted in rats, mice and rabbits by the oral, topical (dermal) and/or subcutaneous routes. Effects noted were umbilical hernia occurred in rats administered with ≥600 mcg/kg, cleft palate in mice administered with 180 mcg/kg subcutaneously, and gallbladder agenesis, umbilical hernia, and flexed front paws in rabbits administered with ≥150 mcg/kg. There were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice.

No toxicological effects unique to mometasone furoate exposure were demonstrated. All observed effects are typical of this class of compounds and are related to exaggerated pharmacologic effects of glucocorticoids.

The carcinogenicity potential of inhaled mometasone furoate (aerosol with CFC propellant and surfactant) at concentrations of 0.25-2.0 mcg/L was investigated in 24-month studies in mice and

rats. Typical glucocorticoid-related effects, including several non-neoplastic lesions, were observed. No statistically significant dose-response relationship was detected for any of the tumor types.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Benzalkonium chloride
Glycerin
Microcrystalline cellulose 65 cps
Citric acid monohydrate
Purified water
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months
Once opened, the product should be used within two months.

6.4 Special precautions for storage

Keep at room temperature below 25°C. Do not freeze.
Protect from direct sunlight.

6.5 Nature and contents of container

In a package with manual dosing, containing 18 g of suspension for 140 actuations.

6.6 Special precautions for disposal and other handling

There are no special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

227/86

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 16.12.2010
Date of last renewal :

10. DATE OF REVISION OF THE TEXT