

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF HUMAN MEDICINAL PRODUCT

NAZOSTER® 0.05 % Nasal Spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Mometasone Furoate 50 micrograms

Excipient(s):

Benzalkonium Chloride 0.02 miligram

Each spray provides 100 mg suspension, equivalent to 50,00 mcg anhydrous mometasone furoate.

3. PHARMACEUTICAL FORM

Nasal suspension, administered with a metered spray pump

White colored aqueous suspension, homogenous on shaking.

4. CLINICAL CHARACTERISTICS

4.1 Therapeutic Indications

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

NAZOSTER® is indicated in the prophylaxis of seasonal allergic rhinitis in adults and in adolescents of 12 years of age and over.

NAZOSTER® may be used in allergic rhinitis in children from 2 to 6 years of age.

Prophylactic treatment must be initiated 2-4 weeks prior to the expected start of the pollen season.

In addition, NAZOSTER® is used in the treatment of symptoms of nasal polyps, such as congestion and loss of smell sensation, in adults of 18 years of age and over.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

In the first use or in case spray pump is not used for a term of 14 days and over, in order to adjust spray pump before use, the drug must be sprayed generally twice until a regular spray is seen. Each spray contains approximately 100 mg mometasone furoate suspension, comprising mometasone furoate monohydrate, equivalent to 50 micrograms of mometasone furoate. In case spray pump is not used for 14 days or more, prior to the next use, the pump is sprayed twice and is adjusted until spray is seen.

Seasonal allergy or perennial rhinitis:

Adults (including elderly patients) and adolescents: For prophylaxis and treatment, generally recommended dose is a total of 200 micrograms, consisting of two sprays to each nostril (50 micrograms/1 spray) once-a-day. After the control of symptoms, maintenance dose may be decreased to 100 micrograms, consisting of one spray to each nostril.

In case symptoms are not sufficiently controlled, daily maximum dose may be increased to a total of 400 micrograms, consisting of four sprays to each nostril.

After control of symptoms, it is recommended to decrease the dose.

Children aged between 2 and 11 years: Recommended dose is a total of 100 micrograms, consisting of one spray to each nostril (50 micrograms/1 spray) once-a-day.

NAZOSTER® has an onset of action 12 hours after the first dose in some patients with seasonal allergic rhinitis. Full treatment may not show benefits within the first 48 hours. Therefore, the patient must maintain treatment to provide full therapeutical benefits.

Nasal polyposis treatment:

Adults (including elderly patients) and adolescents of 18 years of age and over:

Recommended dose is a total of 200 micrograms, consisting of one spray to each nostril (50 micrograms/1 spray) once-a-day. In case symptoms can not be sufficiently controlled within 5 to 6 weeks, the maximum daily dose may be increased to a total of 400 micrograms, with two sprays to each nostril. Dose must be adjusted to the lowest dose, providing effective control of symptoms. In case no improvement in symptoms is seen within 5-6 weeks with twice-a-day administration, alternative treatment must be considered.

The studies of mometasone furoate for nasal polyposis treatment, have lasted 4 months.

Method of administration:

NAZOSTER® is used by spraying to nostrils.

Before administering the first dose, shake the pump well and spray 10 times until a proper spray is observed. In case the pump is not used for 14 days or more, spray pump twice until a proper spray is observed. Shake spray pump mildly before each use. You may discard the spray pump 2 months after first use or after a pre-defined number of sprays.

Additional information for special populations:

Kidney/liver failure: There is no data concerning use in patients with kidney or liver failure.

Pediatric population: Systemic effects of nasal corticosteroids may be particularly seen at prolonged treatments and high doses. Growth retardation has been reported in children, receiving authorized doses of nasal corticosteroids. It is recommended to regularly monitor the

heights in children, receiving prolonged treatment with nasal corticosteroids. If the growth is retarded, the treatment must be revised to decrease the nasal corticosteroid dose to the minimum dose, providing effective symptom control. In addition, the referral of the patient to a pediatrician must be considered.

Geriatric population: Nasal polyposis treatment for geriatric population is just like adults.

4.3. Contraindications

Must not be used in case of hypersensitivity to any components of NAZOSTER®.

NAZOSTER® must not be used in case of presence of untreated localized infections, related to nasal mucosa.

Due to inhibitory action of corticosteroids on wound healing, nasal corticosteroids must not be used in patients, who have had nasal surgery or trauma, before the healing of the wound.

4.4. Special warnings and special precautions for use

NAZOSTER® must be used cautiously in patients with active or latent respiratory tract tuberculosis infections, untreated fungal, bacterial or systemic viral infections or ocular herpes simplex infection.

After 12-month treatment with mometasone furoate, no symptoms of atrophy has been seen in nasal mucosa, at the same time, mometasone furoate has shown a tendency to transform nasal mucosa to normal histological phenotype. As in all long-term treatments, the patients, using NAZOSTER® for a few months or more, must be controlled for possible mucosa changes. In case localized fungal infection develops in the nose or pharynx, it may be necessary to discontinue treatment with NAZOSTER® and to administer appropriate treatment. Persistent irritation in nasopharynx may require discontinuance treatment with NAZOSTER®.

NAZOSTER® will provide control on nasal symptoms in the majority of patients; however, concomitant use of an additional appropriate treatment may also provide additional improvement in other symptoms (in particular eye symptoms).

There is no evidence for suppression of hypothalamus-pituitary-adrenal (HPA) axis with prolonged use of mometasone furoate. However, caution is required for patients, who have initiated NAZOSTER® following prolonged use of systemic corticosteroids. In these patients, discontinuance of systemic corticosteroids may result in adrenal insufficiency symptoms until the functions of HPA axis recover. In case these patients show symptoms of adrenal insufficiency, systemic corticosteroid treatment must be maintained and other treatment methods and necessary measures must be applied.

During transition to NAZOSTER® from systemic corticosteroids, although improvement in nasal symptoms is seen in some patients, they may complain from systemic corticosteroid withdrawal symptoms (e.g., joint and/or muscle pain, fatigue and initially depression). In this case they must be recommended to continue treatment with NAZOSTER®. Such transition may also cause the emergence of allergic conditions, such as conjunctivitis and eczema, which existed, yet suppressed with systemic corticosteroid treatment.

Safety and efficacy of mometasone furoate in the treatment of unilateral polyps, polyps, related to cystic fibrosis or polyps blocking nostrils completely.

Unilateral polyps, which have an extraordinary or irregular appearance, in particular ones with ulceration or hemorrhage must be further examined.

Potentially immunosuppressed patients, who use corticosteroids, must be warned against the risk of contraction of certain infections (e.g., measles, chickenpox) and it must be stressed that medical assistance must be sought.

Following intranasal corticosteroid use, very rare cases of nasal septum perforation or increase in intraocular pressure, has been reported.

No studies concerning efficacy and safety of mometasone furoate in the treatment of nasal polyps in children and adolescents below the age of 18, have been made.

Systemic effects of nasal corticosteroids may be particularly seen at prolonged treatments and high doses. They are seen less frequently compared to oral corticosteroids and varies between persons and the used corticosteroids. Potential systemic effects comprise Cushing's Syndrome, Cushingoid appearance, adrenal suppression, retardation of growth in children and adolescents, cataract, glaucoma and rare physiological behavioral changes, including hyperactivity, sleep disorders, anxiety, depression and aggression (in particular in children).

It is recommended to regularly monitor the heights in children, receiving prolonged treatment with nasal corticosteroids. If the growth is retarded, the treatment must be revised to decrease the nasal corticosteroid dose to the minimum dose, providing effective symptom control. In addition, the referral of the patient to a pediatrician must be considered.

Doses, higher than recommended, may cause clinically significant adrenal suppression. In case there is evidence, pointing that higher-than-recommended doses are used, additional systemic corticosteroid use must be contemplated in terms of surgery or stress.

Excipient:

Benzalkonium Chloride: NAZOSTER[®] contains benzalkonium chloride. 1 g contains benzalkonium chloride, equivalent to 0.2 mg. This amount is not expected to cause bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

A clinical interaction study of mometasone furoate with loratadine, has been made. In these studies, the plasma concentrations of mometasone furoate, were below limit of detection in sensitive analyses with detection limit 50 pg/ml.

4.6 Pregnancy and lactation

General recommendation

Pregnancy Category is C.

Women with childbearing potential/ Contraception

There is insufficient data concerning use on women with childbearing potential.

Pregnancy

No sufficient and controlled studies have been conducted on pregnant women. Just like other

nasal corticosteroid preparations, when deciding to use NAZOSTER® in pregnant women, possible damages on the mother and fetus must be compared with expected benefits. The children of mothers, who have received corticosteroid treatment during pregnancy, must be monitored closely for hypoadrenalism.

Lactation

Just like other nasal corticosteroid preparations, when deciding to use NAZOSTER® in lactating women, possible damages on the mother and fetus must be compared with expected benefits.

Fertility

There is insufficient data concerning the effects of mometasone furoate on fertility of humans.

4.7. Effects on ability to drive vehicles and operate machinery

Its effects on driving and operating machinery are unknown.

4.8. Undesired effects

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); unknown (unpredictable with the available data).

- Undesired treatment related events, reported in adult and adolescent patients with allergic rhinitis, are given below:

Respiratory, thoracic, and mediastinal disorders:

Common: Epistaxis, pharyngitis, nasal burning, nasal irritation and nasal ulceration.

Musculoskeletal, connective tissue, and bone disorders:

Unknown: Retardation in growth rate in prolonged use in children.

It is recommended to monitor the heights of children, receiving prolonged treatment with nasal corticosteroids.

General disorders and administration site conditions:

Common: Headache

Epistaxis is generally mild and resolves spontaneously. Although incidence is higher (5 %) compared to placebo it is comparable to active control nasal corticosteroids (up to 15 %), subject to comparison and it is lower. The incidence of all other effects are comparable to placebo.

In pediatric patients, adverse effect incidence, for example, headache (3 %), epistaxis (6 %), nasal irritation (2 %) and sneezing (2 %) are comparable to placebo.

- Nasal Polyposis: In patients, treated for nasal polyposis, the overall frequency of adverse events is comparable to placebo and is similar to that, seen in patients with allergic rhinitis. In clinical studies for polyps, adverse treatment-related events, reported in 1 % or more of patients, are as follows:

Respiratory, thoracic, and mediastinal disorders:

Very common: Nose bleeding, with 200 micrograms twice-a-day.

Common: Upper respiratory tract infection, with 200 micrograms once-a-day, nose bleeding, with 200 micrograms once-a-day

Uncommon: Upper respiratory tract infection, with twice-a-day 200 micrograms

Gastrointestinal disorders:

Common: Throat irritation: with 200 micrograms twice a day.

General disorders and administration site conditions:

Common: Headache: With 200 mcg once-a-day, with 200 mcg twice-a-day.

Rarely, hypersensitivity reaction (such as bronchospasm, dyspnea) may occur following intranasal administration of mometasone furoate monohydrate. Anaphylaxis and angioedema have been reported very rarely.

Very rarely, taste and smell disorders have been reported.

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

Systemic effects of nasal corticosteroids may be particularly seen when prescribed at high doses for prolonged treatment terms.

4.9. Overdose and Treatment

Since the systemic bioavailability of mometasone furoate is < 1 % (with sensitive devices with detection limits of 0.25 pg/ml), overdose of NAZOSTER® does not require any measures, other than monitoring the patient and then initiation of the correct prescribed dose. Inhalation or oral administration of high doses of corticosteroids may suppress the function of HPA axis.

5. PHARMACOLOGICAL CHARACTERISTICS**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Decongestants and Other Topical Nasal Preparations-Corticosteroids.

ATC code: R01AD09

Mometasone furoate is a topical glucocorticosteroid, with local antiinflammatory characteristics at doses, which are not systemically effective.

Possibly the mechanism of antiallergic and antiinflammatory action of mometasone furoate is based on inhibition of mediators of allergic reactions. Mometasone significantly inhibits the secretion of leukotrienes from leukocytes of allergic patients.

In cell cultures, mometasone furoate has shown high efficacy in the inhibition of IL-1, IL-6 and TNF α synthesis and release and in addition is a potent inhibitor of leukotriene production. In addition, it is a potent inhibitor of Th2 cytokines, among CD4⁺ cells and IL-4 and IL-5 production.

In nasal antigen challenge tests, mometasone furoate has shown antiinflammatory action both in early and late allergic response. This has been shown with a decrease in histamine and eosinophil activity (compared to placebo) and a decrease in epithelial cell adhesion proteins (compared to baseline).

In 28 % of patients with seasonal allergic rhinitis, clinically significant action starts 12 hours after the first dose. Mean improvement onset time (50 %) is 36.9 hours.

In two studies, conducted on 1954 patients, twice-a-day mometasone furoate 200 micrograms has been effective in clinically significant improvement of rhinosinusitis symptoms during a treatment term of 15 days, compared to placebo (P02683, $p<0,001$; P02692, $p=0.038$). In this study, the assessment has been made using the Major Symptom Score (MSS) scale, concerning the symptoms (pain in face/pressure sensation, sensitivity, sinus headache, nasal discharge, discharge to the back of throat and nasal congestion, fullness). Amoxicillin arm in the form of 500 mg thrice-a-day, did not show significant differences from placebo, when considered with respect to MSS. SNOT-20 HRQL, mometasone furoate has shown significant improvement at twice-a-day 200 mcg doses compared to placebo ($p=0.047$). In addition in the post-treatment monitoring term, the rate of relapse, seen with mometasone furoate was low and was comparable to amoxicillin and placebo groups: In acute sinusitis, treatment, exceeding 15 days, has not been examined.

In a placebo-controlled clinical study, conducted on pediatric patients (49 patients in each group) mometasone furoate 100 micrograms has been administered once-a-day for one year and a decrease has not been observed in growth rate.

Data concerning efficacy and safety of mometasone furoate in children of 2 years of age and below, is limited and appropriate dosage range can not be established. In a study, conducted on 48 children between 3-5 years of age treated with intranasal mometasone furoate 50, 100 or 200 micrograms/day for 14 days, no significant change compared to placebo has been seen in mean change in plasma cortisol level as a response to tetracosactrin stimulation test.

5.2 Pharmacokinetic properties

General characteristics

Absorption: The systemic bioavailability of nasally administered mometasone furoate is < 1% when sensitive analyses with detection limit of 0.25 pg/ml are used. Gastrointestinal absorption of mometasone furoate suspension is very low.

Distribution: Not available since administered via nasal route.

Biotransformation: Small quantity, which may be swallowed or absorbed is subject to significant first pass effect in liver.

Elimination: Excreted through urine and bile.

Linearity/non-linear case: No data is available.

5.3. Pre-clinical safety data

Preclinical studies have shown that mometasone furoate did not have estrogenic or antiestrogenic action, yet as other glucocorticoids, it had some antiuterotrophic action and in animal models at high oral doses of 56 mg/kg/day and 280 mg/kg/day, delayed the dilatation of vagina.

Just like other corticosteroids, mometasone furoate has shown clastogenic potential in vitro at high concentrations. However, mutagenic effects were not observed in therapeutically equivalent doses

At a dose of 15 micrograms/kg, an increase in gestation time and an increase in time and difficulty of labor and a decrease in surviving offsprings and body weight and body weight gain were seen. It had no effects on fertility.

Just like other glucocorticoids, mometasone furoate is teratogenic in rodents and in rabbits. Teratology studies have been conducted on rats, mice and rabbits by administering drugs via oral, topical (dermal) and/or subcutaneous routes. Observed effects are umbilical hernia at rats, administered ≥ 600 micrograms/kg, cleft palate at mice administered 180 micrograms/kg and gallbladder agenesis, umbilical hernia and bent front veils at rabbits, administered ≥ 150 micrograms/kg. At the same time, in rats, rabbits and mice, a decrease in maternal body increase, effect on fetus development (low fetal weight and/or ossification delay) and decrease in number of surviving offsprings in mice, is seen.

No toxicological effects, specific to exposure to mometasone furoate, were seen. All observed effects are peculiar to corticosteroid class of drugs and are related to extreme pharmacological effects of corticosteroids.

Carcinogenic potential of mometasone furoate, administered via inhalation (CFC propellants and surfactant aerosol), have been studied on 24-month studies on mice and rats at concentrations of 0.25 to 2.0 micrograms/l. Typical effects, related to glucocorticoids have been observed, including a few non-neoplastic lesions. No statistically significant dose-response relationship was observed in none of the tumor types.

6. PHARMACEUTICAL CHARACTERISTICS

6.1 List of excipients

Dispersible cellulose 65 cps
Glycerin
Citric acid monohydrate
Sodium citrate dihydrate
Polysorbate 80
Benzalkonium Chloride
Phenylethyl alcohol
Deionized water

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

24 months.

6.4. Special warnings for storage

Must be kept in original package at room temperature under 25°C and must not be frozen.

6.5. Nature and content of the package

100 mg suspension in opaque white colored plastic bottle with spray valve with white colored plastic protective cap, in a box.

6.6. The disposal of remnants of human medicinal product and other special precautions

No specific requirements.

Unused products or waste materials must be disposed in accordance with “Regulation concerning Control of Medical Wastes” and

"Regulation concerning Control of Package Wastes."

7. AUTHORIZATION HOLDER

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8. AUTHORIZATION NUMBER(S)

08.05.2007 - 211/22

9. DATE OF INITIAL AUTHORIZATION/RENEWAL OF AUTHORIZATION

Initial authorization date: 08/05/2007

Date of authorization renewal: 23/02/2014

10. DATE OF RENEWAL OF SUMMARY OF PRODUCT CHARACTERISTICS

23/02/2014