1. NAME OF THE PRODUCT

NASODREN®
Powder for the preparation of an intranasal spray.

2. COMPOSITION

INGREDIENT:

A lyophilized powder which is obtained from a natural extract of fresh tubers of Cyclamen europaeum L.
The powder is porous, hygroscopic and cream-coloured.
EXCIPIENTS:

There are neither artificial ingredients nor preservatives.

A solvent (5 ml of purified water) is provided for reconstitution of the lyophilized powder.

Each dose of nasal spray releases 0.13 ml (2-3 drops) of solution (pH 5.3-6.8). This quantity corresponds to 1.3 mg powder. The finished solution produces 38 doses to be applied for a maximum of 16 days.

3. PRODUCT PREPARATION

Nasodren is a nasal spray, to be prepared by dissolving the powder in the purified water and screwing the spray nozzle onto the vial.

INSTRUCTIONS FOR PREPARATION:

1. Open the vial containing the powder by turning the cap counter-clockwise and removing the stopper.
2. Open the plastic bottle with the liquid by breaking off the upper part.
3. Pour the entire liquid into the vial with the powder.
4. Screw the spray nozzle onto the vial and shake gently until fully dissolved. Wait until no foam is visible.
5. Remove the protective cap from the spray nozzle.
6. Prior to the first administration, press the spray nozzle 2-3 times, aiming it away from the body into the air, avoiding the eyes!
HOW TO USE NASODREN®

7. Hold your head vertically; do not lean forwards or backwards. Insert the spray nozzle into the right nostril. Stop breathing for a short time (3-5 seconds) and spray the solution into the right nostril by pressing the spray nozzle once only. Breathe out deeply through the mouth once and then breathe normally. Do not inhale during administering the spray!

8. Then repeat into the left nostril; as described under 7 above.

9. Clean the spray nozzle with a clean paper tissue. Replace the protective cap on the spray nozzle.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NASODREN® is indicated for the symptomatic relief and treatment of diseases of nasal and paranasal cavities, and of the middle ear:

- Acute or chronic recurrent inflammation of the paranasal sinuses (rhinosinusitis): catarrhal or purulent maxillary rhinosinusitis, frontitis, ethmoiditis, sphenoiditis, or combined rhinosinusitis.
- Acute purulent rhinosinusitis, accompanied by generalized infection or orbital complications.
- In case of orbital complications or generalized infection, NASODREN® should be administered in combination with antibiotics.
- Acute exudative or purulent otitis media, chronic exudative, acute secretory otitis media or purulent otitis media. In case of fever, NASODREN® should be administered in combination with antibiotics.
- In postoperative care, after nasal or sinonasal surgery.
4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology in adults and children 5 years old and above:

The solution is sprayed daily only once into each nostril, preferably at the same time of day, approximately 2 hours before bedtime. Increasing the daily dose does not result in an increased effect.

The treatment normally lasts 7-10 days when being used daily but may be extended to 12-16 days if necessary.

A significant improvement or total symptomatic relief is achieved after 6-8 applications; however, headaches often associated with the condition may reduce or stop completely after only 3-5 applications of NASODREN®. Nevertheless, treatment should be continued for the recommended duration of 7-10 days.

In cases which are complicated by purulent infection, concurrent systemic antibiotic treatment is recommended.

If a second treatment is necessary in severe or chronic cases, this should only be initiated 7-10 days after completion of the previous course.

If a dose of the treatment is forgotten, the patient should continue with the treatment the next day as recommended.

4.3 CONTRAINDICATIONS

Individual hypersensitivity against Cyclamen, Primula and other Primulaceae.
4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS OF USE

- Apply only one spray per day into each nostril.
- Avoid inhaling during application.
- Avoid eye contact. Contact of the product with the eyes, resulting in irritation and symptoms of acute conjunctivitis.
- Take note of the section “4.5 Interaction with other products and other forms of interaction”.
- Secondary effects are related to the specific mechanisms of action, and may include some itching, sneezing, a brief sensation of mild to moderate burning in the nasopharynx, reflex salivation and, more rarely, a brief lacrimation and flushing of the face (especially in patients treated with antihypertensive medication). However, these are manifestations of the positive response to the product. [When prescribing NASODREN®, it is suggested that the physician explains these effects to the patients as being due to the stimulation of N. trigeminus and N. facialis, see 5.1 “Product properties”). All these effects usually diminish during the course of treatment.
- In some isolated cases a mild temporary headache or pale pink discharge may appear. It is not necessary to stop treatment in these cases.
- Accidental use by patients allergic to Cyclamen, Primula and other Primulaceae, which could lead to swelling of the nasal mucosa, eyelids and/or face.
4.5 INTERACTION WITH OTHER PRODUCTS AND OTHER FORMS OF INTERACTION

If necessary, other nasal products can be administered 1.5-2h before or after NASODREN®.

Simultaneously administered parasympathomimetic drugs acting either directly (e.g. carbachol, pilocarpine, betanechol), or indirectly (cholinesterase inhibitors like neostigmine, ambenonium etc) will potentiate the effect of NASODREN® (due to amplification of released acetylcholine action in the respective synapses).

After application of NASODREN®, a slight issuing of red blood cells in the nose was observed in some patients. Therefore, treatment with anticoagulants (e.g. coumarin derivatives, acetylsalicylic acid) should be suspended, taking account of the rate of elimination of the particular anticoagulant.

4.6 PREGNANCY AND LACTATION

There is no experience regarding the administration of NASODREN® during pregnancy and breast-feeding in humans. Therefore, NASODREN® should not be administered during pregnancy and breast-feeding, especially during the first trimester.

4.7 EFFECTS ON ABILITY TO DRIVE OR TO OPERATE MACHINERY

Driving or operating machinery is not recommended for 2 hours after using the spray.
4.8 UNDESIRABLE EFFECTS

In very rare cases of prolonged lacrimation or salivation lasting more than 2 hours, give atropine or other anticholinergics such as scopolamine to stop the secretory response.

4.9 OVERDOSE

Exceeding the required dose may cause a severe burning sensation in the nasal mucosa or nasopharynx, without serious consequences. In case of an accidental overdose irrigation of the nasal cavity through the nostrils with warm water, and pharyngeal gargling with warm water can be useful.

5. PRODUCT PROPERTIES

5.1 CHEMICAL COMPOSITION AND PROPERTIES

The extract from the fresh tubers of *Cyclamen europaeum* L. in NASODREN® contains an important saponin fraction. The main saponin component is cyclamin with a triterpenoid structure, which is accompanied by deglucocyclamine, hydrated cyclamine and other structurally related saponins. The cyclamin derived saponins reduce superficial tension of the cell membrane of nasal mucosa and facilitate a direct surfactant effect as the first step. This has been shown in vitro to trigger mucous secretion cells. In addition, the tubers contain small quantities of the glucosides, flavonoids, identified as catechin and epicatechin.

After intranasal administration, the saponins contained in the product attach themselves to the mucosal surface due to their surfactant properties (adsorption) on the nasal mucous membrane. The ability to reach superficial unmyelinated nerve terminals is a property of surfactants in general. Such superficially aimed stimuli initiate an increase in the permeability of the
membrane of nerve terminals to the depolarising sodium ion current, and the resultant influx of Na⁺ produces the “generation potential”. Thus superficial physical impact is converted into a change in electric potential, possibly by reversible stretching or distortion of the terminal axonal membrane, or due to release of neurotransmitters, and results in an increased arterial blood flow, supporting adequate microcirculation.

NASODREN®, on instillation into the nostrils, is not dispersed over the total mucous surface of nasal cavities, nor does it penetrate into the paranasal cavities; instead its initial action is confined to a limited area of the anterior portions of the inferior nasal meatus and of the inferior concha, where, by means of a physical effect, it stimulates the “nociceptive” terminals of the trigeminal nerve; consequently reflex cholinergic responses are elicited. The cholinergic nature of these events was confirmed by means of atropine antagonism, and by potentiation of the response by the acetylcholinesterase inhibitor neostigmine. The reflex character of the response was demonstrated by its elimination with local anaesthetic spray prior to instillation of NASODREN®. Naked endings of the trigeminal nerve are also responsible for initiating sneezing, lacrimation and other reflex responses produced by noxious stimuli, irrespective of their origin. When compared with systemic cholinergic agents, e.g. acetylcholine, neostigmine or pilocarpine by means of histological examination, manifestations of secretory activity appeared considerably more prominent in the case of reflex secretion.

An adequate secretory response is triggered by parasympathetic fibres, which travel in assembly with the facial nerve, and finally reach the nasal and paranasal mucosa. Shortly after the application, a prickly sensation starts, together with a slight to moderate burning in the nose. Repeated, sometimes intense sneezing may occur. An intense reflex secretion that starts a few minutes after application and lasts up to two hours proceeds from epithelial cells lining the nasal and paranasal cavities, including the ostiomeatal unit, and also from the entire submucosal glands. Consequently, prompt discharge, rapid dehydration and reduction of the oedematous state in the
tissues, shrinking of swollen mucosa and opening of the swollen ostiomeatal unit is achieved. This stimulated secretion leads to an intense physiologic drainage of the paranasal sinuses, resulting in a highly effective therapeutic outcome. The saponins are washed out from the nasal cavity by nasal discharge.

The diffuse secretory response to local irritation of the nasal mucosa described above can be considered as a marked “non-adrenergic decongestant effect”. The mode of action is also supported by the histology of the nasal mucosa in rabbits. This demonstrates total exhaustion, or extreme depletion of secretions in superficial goblet cells and glandular epithelium a few minutes after intranasal administration of NASODREN®.

In summary, the clinically proven treatment outcome of rhinosinusitis following NASODREN® can be explained by a “detumescent” effect due to a rapid reflex discharge from hyperplastic/hypertrophic glands around the ostia, the liberation, and consequent facilitated propulsion of exudates out of the nasal and paranasal cavities by means of increased ciliary movement.

NASODREN® is also able to increase ventilation and drainage of the upper respiratory tract. The mechanism of action in otitis media is due to the fact that the auditory tube in its main portion is lined by respiratory type of epithelium, as in paranasal sinuses, and supplied by the same parasympathetic secretory fibres. The reflex discharge of secretions from epithelial and glandular elements in the auditory tube exerts the same draining effect as in paranasal sinuses. In addition, reflex contraction of muscles opening the pharyngeal ostium of the tube (as in deglutition) consequently facilitates the evacuation of the middle ear cavity.

NASODREN® does not cause any significant residual irritation, does not remain in the nasal cavity and does not enter the blood circulatory system.

Clinical data: Phase I to IV studies have been performed. Clinical data in adults and children are available for all indications. In the largest study
published to date, Kryukov and colleagues (2007) randomly allocated 120 patients with rhinosinusitis aged 18-60 years to treatment with NASODREN® monotherapy once daily for 7 days (n=60) or to standard treatment (daily puncture of the maxillary sinus, amoxyclav 1g twice daily, Otrivine® nasal spray 3 times daily, and fexofenadine once daily) for 7 days.

Within minutes of administering NASODREN®, a pronounced rhinorrhoea with secretion of viscous mucus and pus from the nasal cavity was produced. This lasted for about 2 hours. By day 8, 54 of 60 (90%) patients receiving NASODREN® achieved clinical recovery as did all patients treated with standard therapy. Symptoms such as pain, stuffiness and secretion were all significantly improved in the three treatment groups by day 7, as were findings from endoscopic examination such as hyperaemia and oedema.

Interestingly, unlike standard treatment, NASODREN® significantly improved mucociliary clearance in the nasal cavity and paranasal sinuses; this may account for its effectiveness in exudative purulent rhinosinusitis. No side effects were detected in the NASODREN® group.

5.2 PRECLINICAL SAFETY DATA

Acute toxicity in mice was determined via various administration routes. The LD$_{50}$ was determined following oral application by applying 0.2 or 0.5 ml of an undiluted aqueous extract. Both doses resulted in the death of approx. 70% of the animals within three days. At a dilution of 1:5, three out of six mice died; the lowest lethal dose with death rates between 0 and 20% was at 1:20 and/or 1:10 dilution. Consequently, the calculated LD$_{50}$ was 2375 mg/kg; for the pharmaceutical form the LD$_{50}$ = 2386.84 ± 85 mg/kg.

Symptoms exhibited were depression of the central nervous system, phrenospasm, and in some cases diarrhoea. Microscopically, doses of LD$_{50}$ and above produced a swelling of the small intestine and stomach with copious transudation in the intestinal lumen. In addition a significant shrinkage of the spleen occurred (weight 150 ± 4.8 mg [n=6] in the control
group, 72.5 ± 4.1 mg in the intervention group \([p<0.001]\)). The approximate non-toxic dose of the product corresponds to 1/250 \(LD_{50}\) or 10 mg/kg and is 350 times the intranasally applied dose. Extrapolated to the saponin content the oral \(LD_{50}\) amounts to 30-40 ml/kg of the preparation or 1466.46 ± 37 mg/kg.

Intraperitoneal application of various doses of the extract in albino mice resulted in an \(LD_{50}\) of 0.2 ml of the lyophilised extract in a 1:15 - 1:20 dilution, corresponding to 666-500 mg/kg.

Intravenous application of 25 mg/kg led to the immediate death of the animal. The autopsy showed colour changes in the lungs, spleen and liver, corresponding to the haematolytic effect of the saponins. Doses of 5 mg/kg and 10 mg/kg did not lead to death; no macroscopic changes were observed.

Subacute toxicity studies were carried out on mice and rabbits. 0.2 ml of a 0.1% solution, corresponding to the dose applied in practice, which would be accidentally absorbed orally, were applied to mice over 2 weeks. On the 3rd, 7th and 14th day there were no changes in the motor or vegetative functions.

For rabbits the repeated intranasal application of a solution of 1:100 for 5 days did not lead to changes in haemoglobin level or blood count. It did not result in behavioural changes or spontaneous motor activity, or specific signs of a persistent irritation of the nasal mucous membrane of rabbits.

The non-toxic dose of the preparation, corresponding to 1/250 of the \(LD_{50}\), appears to be able to be given without concern, even over a period corresponding to approximately twice the intended clinical duration of application.

The influence on the reproduction capacity of male and female rabbits was investigated during intranasal application of the preparation. Application of dilutions of 1:100 and 1:250 resulted in no indication of an influence on the reproductive capacity of either sex. Likewise, there were no embryotoxic,
fetotoxic or teratogenic effects.

Various studies on the mutagenicity of test subjects for genetic chromosomal mutation showed no indication of mutagenic effects of the cyclamen preparation.

Carcinogenity: No changes were observed in mice after the administration of 10 mg/kg body weight and 100 mg/kg body weight. The mortality in the test group corresponded to the known rate for this species and resulted in no changes in the tumour frequency and distribution vis-à-vis the control group.

Investigations on local compatibility were carried out on the conjunctiva of rabbits as well as the gastric mucous membrane of mice (as a particularly non-sensitive mucous membrane). Therapeutic concentrations were only marginally irritating to the conjunctiva. Various strengths of the preparation induced neither necroses nor cataracts. The gastric mucous membrane proved to be inured to the irritating effects of the preparation, although the typical, previously described dysfunctions of the motor activity were induced in the stomach and small intestine. Moreover, the nasal mucous membrane of rabbits was histologically investigated after intranasal application of the preparation. The nasal mucous membrane was examined 10 minutes after the application of a 1:100 dilution. It showed that the structure of the mucous membrane was maintained, with epithelial cell swelling.

24 hours after repeated administration (5 applications), there were no significant changes in the morphological mucous membrane structure. The secretory element of the epithelium and the submucosal glands recovered. In summary, a high degree of secretory activity was demonstrated, however without indications of inflammation or injury to the mucous membrane surface.
5.3 LIST OF EXCIPIENTS

A solvent (5 ml of purified water) is provided for reconstitution of the lyophilized powder.

5.4 INCOMPATIBILITIES

NASODREN® is incompatible with anticholinergics (such as atropine, tropicamide etc.).

5.5 SHELF LIFE

The expiry date of this product is printed on the carton, the glass vial containing the powder and the purified water. Do not use NASODREN® after the printed expiry date. The prepared solution should be stored in a refrigerator at a temperature of 2-8 °C in a dark place for a maximum of 16 days. Do not use this solution for longer than 16 days.

As a reminder in the package leaflet, the following sentence, for completion by the patient, is included:
“The solution was prepared on: .................. It is stable for 16 days, until: ..................”

5.6 SPECIAL PRECAUTIONS FOR STORAGE

The lyophilized powder and the purified water in their original containers are stable when stored in a dark place and at a temperature less than 25°C. The reconstituted solution must be stored in a refrigerator protected from light at a temperature of 2-8 °C. The product must be stored out of the reach and sight of children.
5.7 **NATURE AND CONTENTS OF CONTAINER**

Procedure pack consisting of one 8 ml vial with the lyophilized powder, one plastic bottle with 5 ml purified water and one dosing pump spray nozzle.

6. **MARKETING AUTHORIZATION HOLDER, MANUFACTURER**

**CE MARK HOLDER:**

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**DATE OF REVISION:**

March 2011

This document follows the classical structure of a “Summary of Product Characteristics (SPC)” document to permit a more comprehensible understanding.

Because NASODREN® achieves its principal action physically, it is classified as Medical Device class I.