SUMMARY OF PRODUCT DEXARIS CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEXARIS (0,2028+0,5) mg/ml, nasal spray, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of suspension contains 0,2028 mg Dexamethasone isonicotinate and 0,5 mg Oxymetazoline hydrochloride.

Pack size of 100 doses
Each spray (of 150 µl) yields 30,4 µg Dexamethasone isonicotinate and 75 µg Oxymetazoline hydrochloride.
Pack size of 300 doses
Each spray (of 50 µl) yields 10,1 µg Dexamethasone isonicotinate and 25 µg Oxymetazoline hydrochloride.

Excipients with known effect: benzalkonium chloride, benzyl alcohol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, suspension
White opalescent homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic rhinitis (hay fever, vasomotor rhinitis), acute rhinitis and nasopharyngitis, sinusitis and nasal polyps.

4.2 Posology and method of administration

Posology
Adults and children over 7 years of age:
Pack size of 100 doses
Unless otherwise prescribed, is sufficient 1 spray (of 150 µl) in each nostril 1-3 times daily..

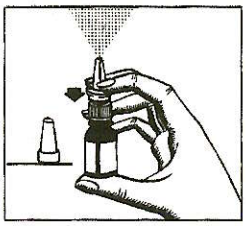
Pack size of 300 doses
Unless otherwise prescribed, are sufficient 2-3 sprays (of 50 µl) in each nostril 1-3 times daily..
Administration to children may be repeated up to 2 times in 24 hours.

Duration of treatment is determined by the treating physician on a case-by-case basis (see section 4.4).
Each course of treatment should not exceed 7 days, unless otherwise directed by the treating physician.
If the doctor recommends prolonged treatment, the nasal mucosa should be checked regularly.

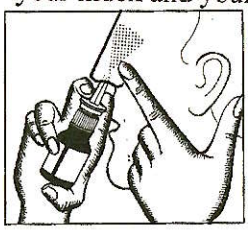
Paediatric population
DEXARIS is contraindicated in children under 7 years of age (see section 4.3).
The administration of DEXARIS to children aged from 7 to 12 years is recommended under adult supervision.
It is recommended to monitor regularly the height of children receiving prolonged treatment with nasal corticosteroids (see section 4.4 Special warnings and precautions for use).

Method of administration
1. Shake well the container.
2. Remove the protective cap from the spray tip.

Before using DEXARIS nasal spray for the first time, the spray pump must be primed so that the product can work properly. For this reason, hold the vial by placing your thumb on the base of the vial and your index and middle fingers on the ring surrounding the nozzle. Make sure that the vial is in an upright position away from your eyes. Squeeze with your thumb, firmly and quickly, the base of the vial 3 times. The pump is now primed and ready for use. If you do not use the product for more than 24 hours, the pump should also be primed until a fine spray is released.



3. Blow your nose to clear the nostrils, if this is necessary..
4. Hold the container in an upright position. Close the one nostril by placing your finger on your nose. Bend your head forward slightly, put the spray tip into the other nostril and squeeze the vial firmly and quickly up with your thumb on the base while holding the pump neck between your index and your middle finger while inhaling slightly through your nose.



5. Repeat step 4 in the other nostril.
6. Do not blow your nose immediately after spraying.
7. The spray tip should be cleaned regularly with warm water.
8. Replace the protective cap.

The vial should be used only by one person, otherwise there is a risk of transmitting viral or bacterial infections.

4.3 Contraindications

DEXARIS should not be used by patients:

- with hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- with untreated infections of nose, mouth, eye and upper respiratory tracts (i.e herpes, cowpox, chickenpox, fungal nasal infection, etc.)
- with tuberculosis
- with dry rhinitis
- with glaucoma (including angle-closure glaucoma)
- after skull surgery through the nasal cavity
- who are taking at the same time monoamine oxidase inhibitors (MAO Inhibitors, tricyclic antidepressants), bromocriptine and other medicines that may potentially increase blood pressure (risk of hypertensive crises – see section 4.5 ''Interaction with other medicinal products and other forms of interaction'').
- with atrophic and vasomotor rhinitis, or rhinitis which is due to mucosa dryness.
- after transsphenoidal hypophysectomy or after surgery in the nasal and oral cavity, to which the dura mater has been exposed, like all other vasoconstrictors.

DEXARIS is not suitable for children under 7 years of age.

Furthermore the product should not be used during pregnancy and lactation (see section 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Prolonged use of vasoconstrictors for nasal administration is not recommended and may lead to chronic inflammation (and therefore nasal congestion and rhinitis medicamentosa) and atrophy of the nasal mucosa.
As with other formulations containing topical vasoconstrictors, DEXARIS should not be used continuously for more than 7 days. If symptoms persist, medical advice is required.
If it is used for more than 7 days, after resolution of the therapeutic effect, significant swelling of the nasal mucosa (nasal edema) may occur as a point of recurrent congestion (rebound effect).
The effect of nasal decongestants may be reduced especially in long-term use and overdose.
Do not use for a long time and do not exceed the recommended dosage.
In case the doctor recommends prolonged treatment, the nasal mucosa should be checked frequently.

Prolonged use of corticosteroids at doses higher than the recommended ones may lead to hypercorticoidism and adrenal insufficiency.
Treatment with higher than recommended doses of nasal corticosteroids 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 scheduled surgeries.

Care should be taken when spraying the medicine so that DEXARIS does not come into contact with the eyes, as this can cause irritation as well as increased intraocular pressure and in exceptional cases cataract.

Due to the potential risk of systemic absorption, DEXARIS should be used with caution and under medical supervision in patients with hypertension, severe cardiovascular diseases, such as coronary artery disease, metabolic disorders such as hyperthyroidism and diabetes mellitus, prostatic hypertrophy, phaeochromocytoma and congenital porphyria.

Caution should be provided in patients receiving MAO inhibitors, tricyclic antidepressants, vasoconstrictors or antihypertensives (see section 4.5 '' Interaction with other medicinal products and other forms of interaction'').

Caution is also required in the elderly and children.

When switching from systemically administered steroids to topical, there is a possibility of adrenal insufficiency, while also any existing allergies may be exacerbated.
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 from patient to patient and among corticosteroid-containing formulations. Potential systemic effects may include Cushing's syndrome, features of Cushing's syndrome, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and, less commonly, a range of psychological and behavioral effects, including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).**

Cushing's syndrome and / or adrenal suppression associated with systemic absorption of topically administered dexamethasone may occur after intensive or long-term continuous treatment in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and compicistat). In these cases, treatment should be discontinued gradually.
Growth retardation has also been reported in children receiving nasal corticosteroids at the recommended doses.
It is recommended to monitor regularly the height of children receiving treatment with nasal corticosteroids for a long period. If growth is slowed down, treatment should be reconsidered in order to reduce the dose of nasal corticosteroid, to the lowest dose that maintains effective symptom control, if it is possible. In addition, the patient should seek the medical advice from a paediatric specialist.

Due to the corticosteroid of DEXARIS, caution should be given to patients with diabetes or osteoporosis, as the risk of infection e.g. tuberculosis, specific viral infections (such as shingles, herpes simplex, vaccinia) or opportunistic infections, may increase.

According to post-marketing experience with dexamethasone products administered orally or parenterally, tumor lysis syndrome (TLS) has been reported in patients with haematological malignancies after the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with a high rate of proliferation, a high tumor load, and a high sensitivity to cytotoxic agents, should be closely monitored and appropriate precautions taken.

DEXARIS contains benzalkonium chloride as a preservative which may cause irritation or swelling inside the nasal mucosa, especially if used for a long time. It also contains benzyl alcohol as a preservative which may cause mild local irritation.

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended concomitant use with Monoamine Oxidase Inhibitors (MAO inhibitors, tricyclic antidepressants), or vasoconstrictors and other drugs that may potentially increase blood pressure ,because due to the effect on the cardiovascular system there is a risk of hypertensive seizures (especially for MAO inhibitors even 15 days after discontinuation of inhibitors).
It is not recommended co-administration with bromocriptine, as there is a risk of hypertensive crisis.
Combined use with tricyclic antidepressants can also lead to arrhythmias.
Caution is required when co-administered with thyroxine.
Interactions with antihypertensives, especially those involving the sympathetic nervous system, can be complex and have a variety of cardiovascular effects.
Use in combination with β2-sympathomimetic drugs may lead to an increased response in β2 agonists.
Cytochrome CYP3A4 inhibitors (i.e ketoconazole, itraconazole, clotrimazole, cyclosporine, ethinylestradiol, troleandromycin, clarithromycin, cimetidine, diltiazem, indinavir including ritonavir or cobicistat): may reduce the clearance of dexamethasone thereby increasing the effects and suppressing the adrenal glands / Cushing's syndrome. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, where patients should be monitored for systemic effects of corticosteroids.
Cytochrome CYP3A4 inducers: Serum levels and / or toxicity of dexamethasone may be reduced when co-administered with cytochrome CYP3A4 inducers (i.e carbamazepine, phenytoin, phenobarbital, rifampicin).

4.6 Fertility, pregnancy and lactation

Oxymetazoline
Data from studies in more than 250 women who used oxymetazoline in the first trimester of pregnancy do not indicate any adverse effects of oxymetazoline on pregnancy or on the fetus / newborn. No relevant epidemiological data are available to date. Animal studies do not show direct or indirect harmful effects with respect to pregnancy, fetal development, parturition or postnatal development. It is not known whether oxymetazoline is excreted in breast milk.
Dexamethasone
The use of DEXARIS is contraindicated during pregnancy or in women who are breast-feeding, due to possible systemic absorption of dexamethasone.

4.7 Effects on ability to drive and use machines

No studies have been performed on the effect to the ability to drive and to use machines. However, patients should be advised that they may experience side effects such as hallucinations, drowsiness, sedation, dizziness and fatigue during treatment with DEXARIS due to dexamethasone.
Systemic effects regarding the circulatory system and the central nervous system can not be ruled out in case of long-term use or at higher than the recommended doses of oxymetazoline.

Therefore, caution is recommended when driving a car or operating machines. If patients experience any of the above side effects they should avoid potentially dangerous activities such as driving or operating machinery.

4.8 Undesirable effects

Prolonged use of corticosteroids, at doses higher than the recommended ones, may lead to systemic symptoms. Growth retardation has been reported in children receiving intranasal steroids.

Immune system disorders
Hypersensitivity (appearance of reactions such as angioedema or skin reactions), masked infection (masking of local infection signs in the ears, nose and larynx)
Disorders of the endocrine system
Semiology of hypercortisolemia, Cushing's syndrome, adrenal suppression (see section 4.4).
Psychiatric disorders
Hallucinations, insomnia, restlessness (mainly in children)
Nervous system disorders
Headache, drowsiness, sedation, dizziness, dysgeusia
Ophthalmic disorders
Increased intraocular pressure, cataract, chorioretinopathy.
Heart disorders
Arrhythmias, tachycardia, palpitations.
Respiratory, thoracic and mediastinal disorders
Nasal septal ulceration and perforation, epistaxis, nasal swelling, nasal discomfort, burning and dryness sensation of the nasal mucosa or mouth, runny nose, sneezing and irritation of the pharynx.
Disorders of the musculoskeletal system and connective tissue
Convulsions (particularly in children)
Gastrointestinal disorders
Nausea
Skin and subcutaneous tissue disorders
Rash, itching, urticaria, clamminess
General disorders and conditions of the route of administration
Fatigue
Paraclinical examinations
Blood pressure increased

Prolonged or excessive use may trigger congestion of nasal mucosa (rebound phenomenon), chronic oedema of nasal mucosa and may cause rhinitis medicamentosa or atrophy of nasal mucosa.

Reporting of suspected adverse reactions
Reporting of 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
National Organization for Medicines
Messogeion 284
15562 Cholargos, Athens
Tel: 213 2040380/337
Fax: 210 6549585
Website: http://www.eof.gr

4.9 Overdose

Oxymetazoline hydrochloride
Overdose may occur after nasal or accidental oral administration. The clinical outcome after poisoning with imidazole derivatives may be unclear due to the occurrence of hyperstimulation episodes alternating with suppression episodes of central nervous system and cardiovascular and pulmonary system.

Symptoms of overdose may be:
hypertension, tachycardia, palpitations, cardiac arrhythmias, cardiac arrest, sweating, agitation, convulsions, mydriasis, nausea, vomiting, cyanosis, fever, convulsions, circulatory shock, pulmonary oedema, respiratory disorders, mental disorders, drowsiness , pallor, miosis, hypothermia, bradycardia, sudden hypotension as in hypotensive shock, respiratory depression and coma.

Pediatric population
In children, in particular, overdose often causes dominant effects on the central nervous system with convulsions and coma, bradycardia, apnoea, as well as hypertension possibly followed by hypotension.

Therapeutic measures after overdose:
Introduction to intensive care is indicated in cases of severe overdose. The administration of medicinal carbon (absorbent), sodium sulfate (laxative) or gastric lavage (in the case of large quantities) should be performed immediately as oxymetazoline can be rapidly absorbed. A non-selective α-inhibitor may be administered as an antidote. If necessary, start fever-reducing measures, anticonvulsant therapy and oxygen therapy. Vasoconstrictors are contraindicated.

Dexamethasone
Chronic abuse and overdose: suppression of the hypothalamic-pituitary-adrenal axis, growth retardation in children.

Treatment
Symptomatic treatment may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and other preparations of the nasal mucosa for topical use - Corticosteroids - Combinations with Dexamethasone
ATC code: R01AD53

Oxymetazoline hydrochloride
Mechanism of action
Oxymetazoline is a derivative of imidazoline. It has a sympathomimetic effect and in particular stimulates the α-adrenergic receptors of the sympathetic system. When administered topically to the nose it causes vasoconstriction of the dilated arteries of the nasopharyngeal mucosa and consequent reduction of blood flow. It also reduces the hypersecretion of the nasal mucosa, ultimately contributing to the decongestion of the nasal mucosa and thus to the normalization of nasal breathing.
Due to the decongestion of the nasal mucosa from the inflammation, the exhaust ducts of the sinuses open and expand and the auditory canal clears. This facilitates the elimination of secretions and fights bacterial invasion.
Pharmacodynamic properties
The antiviral activity of solutions containing oxymetazoline is demonstrated by studies performed with cultures of virus-infected cells (therapeutic approach). This causal mechanism of action has been demonstrated by inhibiting the activity of viruses, e.g. Human Rhinoviruses (HRV) and Influenza-A-Virus.
Antiviral activity was demonstrated using the plaque reduction assay, residual infectivity assay (virus titration), and CPE inhibition assay.
The clinical benefit is not known.
The anti-inflammatory and antioxidant effects of oxymetazoline have been demonstrated in various studies. The production of arachidonic acid lipid mediators is significantly affected by oxymetazoline in ex vivo-stimulated alveolar macrophages.

Due specifically to the oxymetazoline-induced inhibition of 5-lipoxygenase activity, the formation of pro-inflammatory signaling molecules (LTB4) is suppressed, while the synthesis of anti-inflammatory messengers (PGE2, 15-HETE) is increased.
Oxymetazoline also inhibits the inducible form of nitric oxide synthase (iNOS) in long-grown alveolar macrophages.
Oxymetazoline significantly inhibits oxidative stress caused by very fine carbon particles in primary alveolar macrophages.
Oxymetazoline also suppresses lipid peroxidation of microsomes in an iron / ascorbate system (antioxidant activity).
The immunomodulatory effects of oxymetazoline have been demonstrated in human peripheral blood mononuclear cells (PBMCs). Here, oxymetazoline significantly reduces the formation of inflammation-promoting cytokines (IL-1β, IL6, TNFα). In addition, oxymetazoline inhibits the immunostimulatory properties of dendritic cells.
Clinical efficacy and safety
Treatment with nasal spray oxymetazoline compared to saline significantly reduced the duration of colds from an average of 6 days to 4 days ($p = 0,001$). This double-blind comparative study with parallel groups was performed in 247 adult patients and showed a faster and better improvement with the use of oxymetazoline in the typical symptoms of acute rhinitis (stuffy nose, runny nose, sneezing, weakness) ($p = 0,05$) due to the combination of vasoconstriction, antiviral, anti-inflammatory and antioxidant activity of oxymetazoline.

Dexamethasone
Dexamethasone is a corticosteroid, which has mainly glucocorticoid action. Dexamethasone-21-isonicotinate is a synthetic corticosteroid ester with anti-inflammatory and anti-allergic properties.

5.2 Pharmacokinetic properties

Oxymetazoline hydrochloride
Oxymetazoline is present in DEXARIS in such a concentration that at the recommended dosage the amount that enters the systemic circulation is negligible.
Following recommended topical use of pharmacodynamically effective doses of oxymetazoline, its relative absorption is not considered common, but cannot be ruled out.
The absorption rate was estimated at 3,5% in a human study .
Maximum plasma concentration was reached after 8 to 10 hours.
The terminal half-life of oxymetazoline was 35 hours, and was excreted in the faeces (1,1% of the administered dose after 48 hours) and in the urine (2,1% of the administered dose after 96 hours).
After oral administration of 1,8 mg (equivalent to 3,6 ml of 0,5 mg / ml oxymetazoline solution) in healthy humans, non-specific ECG changes were detected. Neither blood pressure nor heart rate were affected after administration of the above active substance.
The effect of oxymetazoline occurs within a few seconds (onset of action was measured in an open observational study where the effect was observed after an average of 20,6 seconds. This was verified by a double-blind placebo-controlled study involving 247 patients where the mean onset of action occurred after 25 seconds.
The effect of oxymetazoline lasts up to 12 hours.

Dexamethasone-21-isonicotinate
To date, no pharmacokinetic data are available after nasal administration of dexamethasone isonicotinate. After inhalation approximately 18 mg dexamethasone isonicotinate peak plasma levels of 20 ng / mL are reached. Similarly, plasma levels of 0,02 ng / mL are expected from nasal spray containing 0,02 mg.
It has been reported for the similar corticosteroid beclomethasone dipropionate that overall systemic bioavailability after nasal administration was even lower compared to inhalation (44 vs. 62%). This is mainly due to the absorption of the ingested fraction and not to the absorption through the nasal mucosa.
In humans, after inhalation using a fixed dose aerosol, dexamethasone-21-isonicotinate is slowly absorbed by the lungs and then slowly removed.

Dexamethasone-21-isonicotinate is hydrolyzed by esterases in the blood and other body fluids to form dexamethasone and isonicotinic acid.
Dexamethasone is rapidly absorbed from the gastrointestinal tract. Its biological plasma half-life is approximately 190 minutes. Plasma protein binding of dexamethasone is approximately 77%, which is lower than that of most corticosteroids. Up to 65% of the dose is excreted in the urine within 24 hours. The clearance in premature infants is reported to be proportional to the duration of pregnancy, with a reduced rate of elimination in most premature infants. It penetrates the placenta rapidly with minimal inactivation.

5.3 Preclinical safety data

Preclinical safety studies in combination with a predetermined dose of oxymetazoline (hydrochloride) and dexamethasone-21-isonicotinate are not available. The following results are available for each active substance alone.

Oxymetazoline hydrochloride
From the acute toxicity studies it was found that LD_{50} for muscle was 9.2 mg / kg after IV administration and 26 mg / kg after per os administration.
The LD_{50} for rats was found to be 0.9 mg / kg after IV administration and 1.3 mg / kg after per os administration.
Repeated dose toxicity studies with nasal oxymetazoline in dogs did not reveal any safety hazards in humans.
An *in vitro* bacterial mutagenicity test (Ames test) was negative. No data are available on carcinogenesis.
No teratogenic effects were observed in rats and rabbits. Doses that exceed the therapeutic range have had lethal effects on fetuses or led to delayed fetal development. Milk production is inhibited in rats. There are no signs of fertility disorders.
Preclinical studies indicate that *benzalkonium chloride*, as a function of concentration and time, can cause an inhibitory effect on the mobility of the fringes up to its irreversible cessation, as well as histopathological changes of the nasal mucosa.

Dexamethasone
Dexamethasone-21-isonicotinate showed low toxicity in relevant toxicity studies with single intraperitoneal administration to mice. In toxicity studies with repeated oral administration in rats and dogs for up to three months, corticosteroid pharmacodynamic effects such as atrophy of the thymus gland and adrenal glands were observed, but not in severe target organ toxicity.
Dexamethasone-21-isonicotinate was not mutagenic *in vitro* (AMES test) and *in vivo* (in the bone marrow micronucleus assay in rats). No carcinogenicity studies are available.
Dexamethasone-21-isonicotinate was teratogenic in rats and rabbits when administered subcutaneously. Teratogenesis is also known from other glucocorticoids (an effect that occurs with this class of substances).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate, Sodium dihydrogen phosphate dihydrate, Carmellose sodium, Benzyl alcohol, Polysorbate 80, Benzalkonium chloride, Sodium hydroxide/Hydrochloric acid, Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25° C.

6.5 Nature and contents of container

15 ml amber glass vial fitted with a dosing pump delivering 100 doses of 150 µl.
15 ml amber glass vial fitted with a dosing pump delivering 300 doses of 50 µl.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Nassington Ltd
3[A] Ippokratous str.
Akropoli, 2006,
Nicosia, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

True translation of the attached document from Greek into English.
Kifissia, 08.06.2023
The Lawyer verifying the translation and declaring good knowledge of both languages

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