PHARMACEUTICALS LIMITED

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) of Nosdrine Plus (Loratadine 5mg + Pseudoephedrine 15mg) Syrup

DGF Drugfield PHARMACEUTICALS LIMITED

1. NAME OF THE MEDICINAL PRODUCT
Nosdrine® - Plus (Loratadine 5mg + Pseudoephedrine 15mg) Syrup.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml Syrup contains:
LORATADINE 5mg
PSEUDOEPHEDRINE HCL 15mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form
Liquid (Syrup)

4. Clinical particulars

4.1 Therapeutic indications

Loratadine and pseudoephedrine combination is used to relieve symptoms of allergies and cold, including runny or stuffy nose, sneezing, watery eyes, and itching of the eyes, nose or throat. It also helps reduce swelling of the nasal passages and restores easier breathing through the nose

4.2 Posology and method of administration

Posology

Syrup:

12years and above: 1teaspoonful (5ml) Syrup to be taken every 12hours

Maximum Dose
2teaspoonful (10ml) per 24hours

Method of Administration
For Orally Administration

4.3 Contraindications

Do not take Nosdrine® Plus Syrup - If you are allergic (hypersensitive) to loratadine, pseudoephedrine or to any of the other ingredients of this medicine.

Due to the presence of pseudoephedrine, do not take Nosdrine® Plus Syrup - If you are also receiving heart or blood pressure medicine. - If you have glaucoma, difficulty in urinating, urinary tract blockage, high blood pressure, heart or blood vessel disease, a history of stroke, or an overactive thyroid. - If you are receiving monoamine oxidase (MAO) inhibitor therapy or have stopped taking this medicine within the last 14 days. Warnings and precautions certain conditions may make you unusually sensitive to the decongestant pseudoephedrine contained.

4.4 Special warnings and precautions for use

Certain conditions may make you unusually sensitive to the decongestant pseudoephedrine contained in this medicine. Talk to your doctor or pharmacist before taking Nosdrine® Plus Syrup:

- If you are 60 years of age or older, older adults may be more sensitive to the effects of this medicine.
- If you have diabetes mellitus (sugar diabetes), stenosing peptic ulcer (ulcer leading to the narrowing of the stomach, small intestine or esophagus), pyloroduodenal blockage (intestine blockage), blockage of the vesical cervix (bladder neck blockage), previous history of bronchospasm (difficulty breathing due to tightening of the lung muscles), or problems with your liver, kidney, or bladder.
- If you are scheduled to have surgery, because you may have to stop taking Nosdrine® Plus Syrup for a few days.
- If you are taking digitalis, a medicine used to treat certain heart disorders, because the dosage may have to be adjusted. - Methyldopa, mecamylamine, reserpine, veratrum alkaloids and guanethidine for blood pressure, because the dose may need to be adjusted.
- If you are taking decongestants (oral or nasal), appetite suppressants (diet pills), or amphetamines, because together with Nosdrine® Plus Plus, these medications may raise your blood pressure.
- If you are taking ergot alkaloids (such as dihydroergotamine, ergotamine, or methylergometrine) for migraines. Together with Nosdrine® Plus, these medications may raise your blood pressure
- If you are taking linezolide (an antibiotic), bromocriptine (for infertility or Parkinson's disease), cabergoline, lisuride and pergolide (for Parkinson's disease). Together with Nosdrine® Plus Syrup, this medication may raise your blood pressure.
- If you are taking antacids, because they may increase the effectiveness of Nosdrine® Plus Syrup. - You are taking kaolin, because it may lower the effectiveness of Nosdrine® Plus Syrup.
  If you have signs and symptoms such as fever, erythema, or small (generalized) pustules, you should discontinue using the drug and consulting your physician. Do not give this medicine to children less than 12 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

- When administered concomitantly with alcohol, loratadine has no potentiating effects as measured by psychomotor performance studies.
- Cytochrome(CYP3A4 and CYP2D6) inhibitors have been shown to increase loratadine and desloratadine exposure. However, due to the wide therapeutic index of loratadine, concurrent administration of monoamine oxidase inhibitors (reversible or irreversible) and sympathomimetic medicines can cause critical hypertension reactions. Sympathomimetic medicines may reduce the effect of antihypertensive medicines.
- The following combinations are not recommended: Bromocriptine, cabergoline, lisuride, pergolide: risk of vasoconstriction and increase in blood pressure.

- Dihydroergotamine, ergotamine, methylergometrine: risk of vasoconstriction and increase in blood pressure. Reversible and irreversible MAO inhibitor(s): risk of vasoconstriction and increase in blood pressure. Other vasoconstrictors used as nasal decongestant, by oral or nasal route, (such as phenylpropanolamine, phenylephrine, ephedrine, oxymetazoline, naphazoline): risk of vasoconstriction.
- Antacids increase the rate of pseudoephedrine sulphate absorption, kaolin decreases it.
- Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic).

KEEP OUT OF THE REACH OF CHILDREN!

4.6 Fertility, pregnancy and lactation

Pregnancy:
Do not use Nosdrine Plus during pregnancy.
The use of pseudoephedrine decreases maternal uterine blood flow. The use of Nosdrine Plus is contraindicated during pregnancy.

Lactation:
Loratadine and Pseudoephedrine is excreted is breast milk, therefore the use of Nosdrine Plus is not recommended in breast-feeding women.

4.7 Effects on ability to drive and use machines

In clinical trials that assessed driving ability, no impairment occurred in patients receiving loratadine. However, some people very rarely experience drowsiness, which may affect their ability to drive or use machines. It is not expected that pseudoephedrine sulphate impairs psychomotor performance.

4.8 Undesirable effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Contact a doctor or pharmacist immediately if you have any reaction to Nosdrine® Plus that continues, is bothersome or that you think is serious.

- Very common side effects (may affect more than 1 in 10 people) associated with Nosdrine® Plus include: trouble sleeping.
- Common side effects (may affect up to 1 in 10 people) associated with Nosdrine® Plus include: thirst, nervousness, drowsiness, depression, agitation, anorexia, dizziness, dry mouth, fast heartbeat, sore throat, inflammation of the nasal lining, constipation, nausea, headache and tiredness.
- Side effects occurring less frequently include: confusion, tremor, increased sweating, hot flushes, altered taste, abnormal tearing of the eyes, ringing in the ears, irregular heartbeat, nosebleed, frequent or abnormal urination and itching.

- From post-marketing experience, isolated cases of acute generalized exanthematouspustulosis (AGEP), a form of severe skin reaction, have been reported with pseudoephedrine-containing products.

The following very rare side effects (may affect up to 1 in 10,000 people) have also been seen during the marketing of Nosdrine® Plus Syrup: severe allergic reaction including rash, hives, and swelling of the face, vertigo, convulsions, abnormal heart rhythms, high blood pressure, cough, narrowing of the airways, liver problems, difficulty urinating, and hair loss have been reported. Other adverse reactions that were only reported for loratadine in clinical trials and during the post-marketing period include increased appetite, rash and upset stomach.

4.9 Overdose

Loratadine

Overdosage with loratadine increased the occurrence of anticholinergic symptoms. Somnolence, tachycardia, and headache have been reported with overdoses.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

Pseudoephedrine Hydrochloride

Acute overdosage with antihistamines results primarily in central nervous system effects. In the small child, predominant symptoms are excitation, hallucination, ataxia, incoordination, tremors, flushed face and fever. Convulsions, fixed and dilated pupils, coma and death may occur in severe cases.

In the event of overdose, induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Gastric lavage may be carried out. Precautions against aspiration must be taken, especially in infants and small children.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamines – H1 antagonist, ATC code: R06A X13.
Pharmacotherapeutic group: Nasal decongestants for systemic use group, ATC code: R01BA52.

Mechanism of Action

Loratadine is a tricyclic antihistamine with selective, peripheral H1-receptor activity. Loratadine has no significant H2-receptor activity. It does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity.

Pseudoephedrine sulfate (d-isoephedrine sulfate) is a sympathomimetic agent with mostly α-mimetic activity in comparison with the β-activity. Pseudoephedrine sulfate provides a nasal decongestant effect after oral administration due to its vasoconstrictive action. It has an indirect sympathomimetic effect due primarily to the release of adrenergic mediators from the post-ganglionic nerve endings.

Pharmacodynamic effects

The pharmacodynamics of Nosdrine- Plus are directly related to that of its components.

Loratadine has no clinically significant sedative or anticholinergic properties in the majority of the population and when used at the recommended dosage.

During long-term treatment there were no clinically significant changes in vital signs, laboratory test values, physical examinations or electrocardiograms.

Oral administration of pseudoephedrine at the recommended dose can cause other sympathomimetic effects, such as increased blood pressure, tachycardia or manifestations of central nervous system excitation.

5.2 Pharmacokinetic properties

Loratadine

Absorption
Loratadine is rapidly and well-absorbed. Concomitant ingestion of food can delay slightly the absorption of loratadine but without influencing the clinical effect. The bioavailability of loratadine and of the active metabolite are dose proportional. Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic).

Distribution
Loratadine is highly bound (97 % to 99 %) and its active major metabolite desloratadine (DL) moderately bound (73 % to 76 %) to plasma proteins. In healthy subjects, plasma distribution half-lives of loratadine and its active metabolite are approximately 1 and 2 hours, respectively.

Biotransformation
After oral administration, loratadine undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. The major metabolite-desloratadine (DL) is pharmacologically active and responsible for a large part of the clinical effect. Loratadine and DL achieve maximum plasma concentrations (Tmax) between 1–1.5 hours and 1.5–3.7 hours after administration, respectively.

Elimination
Approximately 40 % of the dose is excreted in the urine and 42 % in the faeces over a 10 day period and that, mainly in the form of conjugated metabolites. Approximately 27 % of the dose is eliminated in the urine during the first 24 hours. Less than 1 % of the active substance is excreted unchanged in active form, as loratadine or DL. The mean elimination half-lives are 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the active metabolite.

Renal impairment
In patients with chronic renal impairment, both the area under the curve (AUC) and peak plasma levels (Cmax) increased for loratadine and its active metabolite as compared to the AUCs and peak plasma levels (Cmax) of patients with normal renal function. The mean elimination half-lives of loratadine and its active metabolite were not significantly different from those observed in normal subjects. Haemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite in subjects with chronic renal impairment.

Hepatic impairment
In patients with chronic alcoholic liver disease, the AUC and peak plasma levels (Cmax) of loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function. The elimination half-lives for loratadine and its metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Elderly
The pharmacokinetic profile of loratadine and its metabolites is comparable in healthy adult volunteers and in healthy geriatric volunteers.

Pseudoephedrine Hydrochloride

Absorption
After oral administration, pseudoephedrine sulphate is rapidly and completely absorbed. Onset of action occurs within 30 minutes and a dose of 60 mg has a decongestive action lasting for 4 to 6 hours.
Food may increase the amount of loratadine absorbed, but without clinically significant results. This is not observed with pseudoephedrine.

Distribution
Pseudoephedrine is presumed to cross the placenta and the haematoencephalic barrier. The active substance is excreted in breast milk of lactating women.

Biotransformation
Pseudoephedrine Hydrochloride undergoes incomplete hepatic metabolism by N-demethylation to an inactive metabolite.

Elimination
Its elimination half-life in humans, at an approximate urinary pH of 6, ranges from 5 to 8 hours. The active substance and its metabolite are excreted in urine, 55-75 % of the administered dose is excreted unchanged. The rate of excretion is accelerated and the duration of action decreased in acidic urine (pH5). In case of alkalinization of the urine, a partial resorption takes place.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies, no teratogenic effects were observed. However, prolonged parturition and reduced viability of offspring were observed in rats at plasma levels 10 times higher than those achieved with clinical doses.

6. Pharmaceutical particulars

6.1 List of excipients

Propylene Glycol
Sucrose
Sodium CMC (MV)
Aspartame
Methyl Paraben
Ethanol 96%
Raspberry Essence
Sunset yellow
Citric acid
Butylated Hydroxyaisole (BHA)
Purified water (to the volume)

6.2 Incompatibilities

Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30 °C. Protect from light and moisture.
Store in the original bottle to protect from moisture.

6.5 Nature and contents of container
Nosdrine® Plus Syrup is presented in 60ml bottle covered with a cap containing DGF logo and Drugfield with a measuring device, enclosed in hardboard carton FPP.

6.6 Special precautions for disposal and other handling

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

7.0 Applicant/Manufacturer
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