Physician's Prescribing Information Leaflet

ANTROLIN

Nifedipine 0.3% and Lidocaine Hydrochloride 1.5% Rectal Cream

1) NAME OF THE DRUG PRODUCT: ANTROLIN

2) QUANTATIVE-QUANTITATIVE COMPOSITION: Nifedipine 0.3 % w/w and Lidocaine Hydrochloride 1.5 % w/w.
For the excipients see 6.1

3) PHARMACEUTICAL FORM: Cream for rectal use

4) CLINICAL INFORMATION:
4.1) Therapeutic Indications: Treatment of anal fissures and proctologies generally associated with anal sphincter hypertonia.

4.2) Doses, route and duration of administration: For endorectal and perianal applications. Apply the cream twice a day for at least three weeks (see section 6.6.)

4.3) Contraindications: Hypersensitivity to the active ingredients, particularly to Lidocaine (and other local anesthetics with a similar amidic type structure) or to any other excipient.
Presumed or ascertained pregnancy and breast feeding (see Section 4.6).
Severe hypotension and cardiac insufficiency.

4.4) Warnings and precautions: The topical administration of the drug for excessive and/or prolonged periods may cause sensitivity reactions and local reactions of hyperemia and bleeding that disappear when the treatment is stopped. During the clinical trials no adverse reactions resulting from the systemic absorption of the drug were reported.
ANTROLIN cream for rectal use should be used with caution in patients with severely injured mucosa and phlogosis (inflammation) in the area to treat since this may cause excessive absorption of the active substances.
The drug should be used with caution in diabetic patients or in those with hepatic and/ or renal insufficiency.
The use of ANTROLIN cream for rectal use in elderly patients, in patients under eighteen years of age, or in patients being treated with beta-blockers or antihypertensive drugs should be supervised by the physician.
The arterial pressure should be checked at the beginning and periodically during the treatment.
In case of failure of the therapy (the absence of improvement or worsening of the symptoms) the treatment must be stopped and a physician must be consulted to take other measures.

Warning: ANTROLIN cream for rectal use contains sodium methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions, even delayed. It also contains propylene glycol and cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).

Pediatric population: the safety and efficacy of ANTROLIN in adolescents and children below 18 years of age have not been established

4.5) Drug to drug interactions: Treatment with ANTROLIN rectal cream may increase the effect of antihypertensive drugs due to the presence of Nifedipine. Propranol prolong the plasmatic half-life of Lidocaine and increases the plasmatic levels of Nifedipine. Cimetidine

may increase the plasmatic levels of Nifidipine and Lidocaine. The simultaneous administration of ANTROLIN cream for rectal use in patients in treatment with Digoxin may increase the plasmatic levels of Digoxin.

4.6) Pregnancy and breast feeding: Nifedipine and Lidocaine cross the placental barrier and are excreted in the breast milk. The studies on mice and rabbits have shown that Nifedipine may provoke a teratogenic effects. Lidocaine has not shown any risks to the fetus. However, the product should not be used by pregnant or breast feeding women.

4.7) Effects concerning the capacity to drive and to operate machinery: Nifedipine, if taken orally simultaneously with alcohol may reduce the capacity of reaction. In the case of ANTROLIN cream for rectal use, it is intended to be administered and to effect locally. No effects that could influence the capacity to drive and to operate machinery are therefore foreseeable.

4.8) Side effects: Reactions like pain, a burning sensation, itchiness, hyperemia and bleeding could occur locally. These effects decrease when the treatment is stopped.
In very rare cases, the local application of drugs containing Lidocaine has caused allergic reactions (anaphylactic shock in the most severe cases).
During the clinical trials, no side effects due to a possible systemic absorption of the two active ingredients (headache, vertigo, peripheral vasodilatation, hypotension, dizziness and tremor) were shown.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9) Overdose: No cases of systemic toxicity from an overdose after the topical application of ANTROLIN cream for rectal use have been reported. In the eventuality of intoxication after topical application of the medicine, the systemic effects should be similar to those caused by the active ingredients in other routes of administration.
In cases of severe intoxication from Nifedipine disorders of conscience up to coma, decrease in the arterial pressure, alterations of the heart rate and cardiogenic shock may occur. As regards the treatment, beta-sympathomimetics may be used for bradycardia and in the case of severe hypotension, Calcium Gluconate 10% solution (10-20 ml, slowly intravenous) and eventually Dopamine or Norepinephrine.
Most of the toxic reactions to the local anesthetics and to Lidocaine, in humans, affect the central nervous system; "lightheadedness" and dizziness, often followed by visual and auditory troubles such as accommodation difficulties and tinnitus have been reported. In serious cases, depression of the central nervous system and convulsions may occur. The treatment is symptomatic.

5) PHARMACOLOGICAL DATA:
5.1) Pharmacodynamics properties: Pharmacotherapeutic group: ATC code C05AX - Other agents for the treatment of hemorrhoids for topical use.
The action mechanism of ANTROLIN cream for rectal use is of a synthetic type. Nifedipine, a dihydropyridine with a calcium-antagonist action, if used locally, has a relaxing action on the peripheral smooth musculature. Nifedipine acts by reducing the internal anal sphincter

hypertonia. The action of Nifedipine is supplemented in the drug by Lidocaine, a local topical anesthetic.

5.2) Pharmacokinetic properties: The pharmacokinetic properties of ANTROLIN cream for rectal use have been studied on healthy volunteers. The determination of the active substances in the blood, through a validated analytical method, have had a negative result, as the presence of Nifedipine was not found in any serum. Furthermore, only minimum traces of Lidocaine were found in 2 patients out of 12. These very low concentrations (below the quantization of the method) are however much lower than the therapeutically efficacious ones that can be found after systemic administration. Therefore, it is reasonable to exclude that local administration of ANTROLIN may determine systemic effects consequent to the absorption of its active ingredients. For further confirmation of this, during the clinical trials no adverse reactions due to the systemic absorption of the two active ingredients by the anorectal mucosa were shown.

5.3) Preclinical safety data: A study of acute toxicity, in mice, did not find toxic or lethal effects until administration of 50 times the single therapeutic dose. The tests of subacute toxicity have shown that ANTROLIN cream for rectal use does not significantly change the hemato-chemical parameters of the animals tested and is well tolerated. A study of the irritant potential of ANTROLIN, on rabbits, has classified the medicine as "not irritant".

6) PHARMACEUTICAL INFORMATION:
6.1) Excipients: White Vaseline (= Paraffin, White Soft), Propylene Glycol, Semi-Synthetic Liquid Glycerides (= Triglycerides, Medium-Chain = MCT), Polyethylene Glycol Stearate (= Macrogol Stearate = PEG Stearate), Cetostearyl Alcohol, Glycerol Monostearate, Sodium Methyl Parahydroxybenzoate (= Sodium Methylparaben), Propyl Parahydroxybenzoate (= Propylparaben), Purified Water.

6.2) Incompatibility: Since compatibility tests have not been carried out, the medicine must not be mixed with other products.

6.3) Shelf life: The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: 30 days (one month).

6.4) Special care for the preservation: Keep in tightly closed packaging. Store below 25°C.

6.5) Type and contents of the packaging: A cardboard box containing one aluminum tube 30 g cream and one cannula.

7) ISRAELI MARKETING AUTHORIZATION HOLDER: Super-Pharm (Israel) Ltd., VAT # 510753551, 16 Arie Shenkar Street, Herzliya 4672516.

8) MARKETING AUTHORIZATION NUMBER: Israeli Drug Registration Number: 160.31.34663.00

9) MANUFACTURER: NEW FA DEM Farmaceutici e Chimici S.r.l., Giugliano in Campania (NA), Italy.

10) DATE OF LAST REVISION: The format and contents of this leaflet were determined, checked and approved by the Israeli Ministry of Health on 03/2018
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