Nixoran

Nitazoxanide

Oral use

Film-coated tablets - Suspension

Formulae

Nixoran Tablets: Each film-coated tablet contains Nitazoxanide 500 mg. Excipients: Corn starch; Pregelatinized starch; Hydroxypropylmethylcellulose; Sodium starch glycolate; Talc; Magnesium stearate; Triacetine; Ferric oxide yellow; Titanium dioxide; Polyethylene glycol 6000.

Nixoran Suspension: Each 100 ml of reconstituted solution contains Nitazoxanide 2 g. Excipients: Sodium benzoate; Sucrose; Xanthan gum; Microcrystalline cellulose and Sodium carboxymethylcellulose; Adipic acid; Allura red aluminum lake (FD&C # 40); Strawberry flavor.

Therapeutic Action

Antiparasitic agent.

Indications

Acute intestinal amœbiasis or amœbian dysentery caused by Entamœba histolytica. Amœbian liver abscess. Giardiasis caused by Giardia lamblia. Single or mixed intestinal parasitic infections caused by Enterobius vermicularis, Ascaris lumbricoides, Strongiloides stercolaris, Necator americanus, Ancylostoma duodenale, Trichuris trichiura, Taenia saginata, Taenia solium, Hymenolepis nana, Fasciola hepatica, Isopora belli and Cryptosporidium parvum. Trichomoniasis in women and men. Infections caused by Blastocystis hominis.

Pharmacological Action

Nitazoxanide is a 5-nitrothiazole derivative with broad spectrum antiparasitic and antibacterial activity. It has one pharmaceutically active metabolite: Desacetyl-nitazoxanide or tizoxanide.

Nitazoxanide is effective against a broad range of parasites and bacteriae that infect animals and humans. Its effect has been evaluated on a broad range of parasites, like protozoa, nematodes, cestodes and trematodes so as to support clinical evaluation in humans.

The nitrothiazole ring replaced the nitroimidazole ring (present in metronidazole), so as to avoid mutagenic activity in the Ames test. The sulphur atom that replaces the nitrogen atom within the ring is believed to be responsible for some kind of detoxification of the nitro-derivative of this family of compounds.

The chemical structure of Nitazoxanide was designed based on structure-activity relationships. The antihelmintic activity was based on structure similarity with nitrobenzamide compounds while the nitrobenzene ring is replaced by a nitrothiazole ring, known for its antibacterial and antiprotozoal activity. The decision to use a nitrothiazole ring instead of a nitroimidazole ring was based on toxicology. Nitazoxanide did not show mutagenic activity in a variety of tests while all nitroimidazoles did.

Regarding its antiparasitic mechanism of action, biochemical and electron spin resonance tests showed, in parasites like Trichomonas vaginalis, Giardia intestinalis and, probably, although not scientifically proven, Entamoeba histolytica, that the pyruvate-ferredoxin oxidoreductase (PFOR) and, to a lesser extent, the hydrogenase, reduce ferredoxine which, on its turn, may be oxidized by the nitro group at position 5 of the nitroheterocyclic drugs like Nitazoxanide. In these organisms, Nitazoxanide is reduced to a toxic radical in an organelle of the carbohydrate metabolism, the hydrogenosome, which contains hydrogenase, PFOR and ferredoxine. The mechanism of Nitazoxanide's antihelmintic activity is unknown but it could be similar to that of antihelmintic nitrobenzamides like niclosamide. This type of compounds interferes with the carbohydrate metabolism of helminths by blocking the citric acid cycle, thus leading to the accumulation of lactic acid and consequent death of the parasite.

Pharmacokinetics:

Nitazoxanide's intraluminal antiparasitic effect is due to its incomplete absorption, which also accounts for the fact that it is principally eliminated in feces.

However, the absorbed portion is rapidly metabolized and its active metabolite, desacetyl-nitazoxanide or tizoxanide, which also undergoes conjugation primarily by glucuronidation, is active against the extra-intestinal clinical manifestation of parasitoses.

The parent drug is not detectable in plasma and following oral administration, peak plasma concentration of the active metabolite is achieved within 3-4 hours. Food increases the absorption of Nitazoxanide. It is excreted in the feces and bile (2/3 of the oral dose) and urine (1/3 of the oral dose).

Dosage and Administration

Amœbiasis / cysts and trophozoites: 7.5 mg / kg every 12 hours, during 3 days.
Giardiasis and helminthiasis: 7.5 mg / kg every 12 hours, during 3 days.
Trichomoniasis: 7.5 mg / kg every 12 hours, during 3 days.
Fasciolasis: 7.5 mg / kg every 12 hours, during 7 days.
Nixoran Tablets: 1 tablet = 500 mg of Nitazoxanide.
Nixoran Suspension: 5 ml of suspension = 100 mg of Nitazoxanide.

Following information may be used as dosing guidance:

Tablets:

Adults and children over 16 years of age: One 500 mg Nitazoxanide tablet every 12 hours, during 3 days.
In the case of fasciolasis, the duration of treatment must be of 7 days.
In the case of trichomoniasis, the partner should be treated concomitantly to avoid repeated reinfestations.

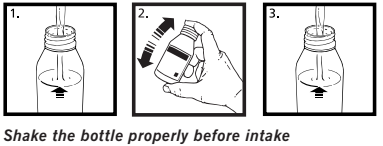
Suspension:

Children between 1 and 3 years of age: 5 ml (100 mg of Nitazoxanide) every 12 hours, during 3 days.
Children between 4 and 11 years of age: 10 ml (200 mg of Nitazoxanide) every 12 hours, during 3 days.
Children between 12 and 15 years of age: 15 ml (300 mg of Nitazoxanide) every 12 hours, during 3 days.
Adults and children over 16 years of age: 25 ml (500 mg of Nitazoxanide) every 12 hours, during 3 days.
In the case of fasciolasis, the duration of treatment must be of 7 days.
In the case of trichomoniasis, the partner should be treated concomitantly to avoid repeated reinfestations.

In order to increase absorption and avoid possible gastrointestinal disorders, it is recommended to take **Nixoran** with food.

Directions for preparation of the solution:

1. Tap bottle to loosen the powder until it flows freely. Add drinking water up to the marking on the label.
2. Close the bottle and shake until complete suspension of the powder.
3. Add water until reaching the marking on the label and shake again.



Shake the bottle properly before intake

The reconstituted suspension may be stored for 7 days at room temperature.

Contraindications

Patients with known hypersensitivity to the active ingredient or to any component of the product. It is not recommended for children under the age of 1 year.

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Warnings and Precautions
Coprological tests should be performed at the end of the treatment in order to determine the complete eradication of mature and immature forms of intestinal parasites.
Pregnancy: Reproduction studies in rats and rabbits at doses 200 times the clinical adult dose revealed no evidence of teratogenicity, embryotoxicity or fetotoxicity. Nevertheless, administration of **Nixoran** during pregnancy, if strictly necessary, should be decided upon by the physician, by evaluating possible benefits and potential risks.
Nursing: As there is no information available concerning excretion of Nitazoxanide in human milk, the physician should ask to stop breast feeding depending on the importance of Nitazoxanide for the mother.
Use in the elderly: Clinical studies with Nitazoxanide performed in elderly patients, did not suggest any need for dose adjustment in these patients. Nevertheless, **Nixoran** should be administered with caution to these patients as some vital functions may be diminished.
Hepatic and renal insufficiency: No clinical studies have been carried out with this group of patients. Therefore, Nitazoxanide should be administered with caution.

Drug interactions
The active metabolite of Nitazoxanide is highly bound to plasma proteins. Caution should be exercised when administering Nitazoxanide to patients treated with coumarins or warfarin as it may increase their plasma levels leading to prothrombin time prolongation. Nitazoxanide has no significant inhibitory effect on Cytochrome P450 enzymes; therefore, interactions with drugs metabolized by these enzymes are not to be expected.

Laboratory test interference:
There is no information available regarding possible interferences of Nitazoxanide with laboratory tests.

Adverse reactions
Adverse reactions reported were, generally, mild and related to the gastrointestinal system.
The most frequently observed were: Abdominal pain, diarrhea, headache, nausea and vomiting.
Less frequently: Anorexia, epigastric pain, vertigo and weakness.
Rarely: Rash and asymptomatic discoloration of urine, semen and the sclerotic were reported, with no pathological relevance and which resolved spontaneously after treatment discontinuation.

Overdosage
Overdosage is very unlikely. Single oral doses of up to 4000 mg Nitazoxanide have been administered to healthy adult volunteers without significant adverse effects. In case of appearance of adverse effects, they would be affecting the gastrointestinal tract. After thorough clinical evaluation of the patient, considering the time lapsed from administration and the amount of drug taken, the physician will decide whether or not to perform the rescue treatment: Gastric evacuation (vomiting or gastric lavage) and administration of aluminum hydroxide with magnesium.

How Supplied
Nixoran Film-coated tablets: Packages containing 6 film-coated tablets.

Yellow oblong tablets, coded NZ on one side of the tablet and marked with Roemmers' identification isologue on the other side.

Nixoran Suspension: Package containing powder for oral suspension 2 g/100 ml (60 ml).
Slightly yellow to pink powder.
Reconstituted suspension: Pink homogeneous suspension.

Dispensed under prescription.
Made in Argentina.

Product authorized by the Ministry of Health.
Certificate Nº 47,595
Technical Director: Jorgelina D'Angelo, Pharmacist.
Last revised: April 2006.

Medicinal product.
Keep out of the reach of children.

Keep in a dry place at temperature below 30°C.
After reconstitution, the suspension may be kept for 7 days at room temperature.

Marketing Authorization Holder:
Roemmers S.A.I.C.F.
Fray Justo Sarmiento 2350,
B1636AKJ Olivos, Buenos Aires, Argentina.

Manufacturer:
Nixoran Film-coated tablets:
Roemmers S.A.I.C.F.
Buenos Aires, Argentina.
Nixoran Suspension:
Dicofar S.R.L.
Buenos Aires, Argentina.

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