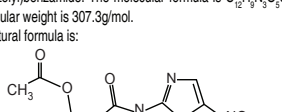
NT-TOX® 500mg Tablets 100mg/5mL For Oral Suspension
(Nitazoxanide)

این ٹی۔ٹوکس ۵۰۰ ایم جی/۵ ایم ایل/۵ ایم ایل لیٹر
(نیٹازوکسانائیڈ) اورل سسپنشن

DESCRIPTION: NT-TOX® Tablets and NT-TOX For Oral Suspension contain the active ingredient, nitazoxanide, a synthetic antiprotozoal agent for oral administration. Nitazoxanide is a light yellow crystalline powder. It is poorly soluble in ethanol and practically insoluble in water. Chemically, nitazoxanide is 2-acetyloxy-N-(5-nitro-2-thiazolyl)benzamide. The molecular formula is $C_{12}H_9N_3O_5S$ and the molecular weight is 307.3g/mol.
The structural formula is:



QUALITATIVE AND QUANTITATIVE COMPOSITION:
NT-TOX Tablets 500mg
Each film-coated tablet contains:
Nitazoxanide..... 500mg
Genix Specification
NT-TOX For Oral Suspension 100mg/5mL
Each 5mL reconstituted suspension contains:
Nitazoxanide.....100mg
Genix Specification

CLINICAL PHARMACOLOGY: Absorption: Following oral administration of NT-TOX Tablets or Oral Suspension, maximum plasma concentrations of the active metabolites tizoxanide and tizoxanide glucuronide are observed within 1-4 hours. Nitazoxanide Tablets are administered with food, the AUC of tizoxanide and tizoxanide glucuronide in plasma is increased almost two-fold and the Cmax is increased by almost 50%. When Nitazoxanide for Oral Suspension was administered with food, the AUCt of tizoxanide and tizoxanide glucuronide increased by about 45-50% and the Cmax increased by ≤10%. **Distribution:** In plasma, more than 99% of tizoxanide is bound to proteins. **Metabolism:** Following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation. In vitro metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes.
Elimination: Tizoxanide is excreted in the urine, bile and feces, and tizoxanide glucuronide is excreted in urine and bile. Approximately two-thirds of the oral dose of nitazoxanide is excreted in the feces and one-third in the urine.
Special Populations: Patients with Impaired Hepatic and/or Renal Function: The pharmacokinetics of nitazoxanide in patients with impaired hepatic and/or renal function has not been studied. **Geriatric Patients:** The pharmacokinetics of nitazoxanide in geriatric patients has not been studied. **Pediatric Patients:** The pharmacokinetics of nitazoxanide following administration of Nitazoxanide Tablets in pediatric patients less than 12 years of age has not been studied. The pharmacokinetics of nitazoxanide following administration of Nitazoxanide Oral Suspension in pediatric patients less than one year of age has not been studied.

MICROBIOLOGY: Mechanism of Action: The antiprotozoal activity of nitazoxanide is believed to be due to interference with the pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction which is essential to anaerobic energy metabolism. Studies have shown that the PFOR enzyme from Giardia lamblia directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The DNA-derived PFOR protein sequence of Cryptosporidium parvum appears to be similar to that of Giardia lamblia. Interference with the PFOR enzyme-dependent electron transfer reaction may not be the only pathway by which nitazoxanide exhibits antiprotozoal activity. **Activity in vitro:** Nitazoxanide and its metabolite, tizoxanide, are active in vitro in inhibiting the growth of (i) sporozoites and oocysts of Cryptosporidium parvum and (ii) trophozoites of Giardia lamblia. **Drug Resistance:** A potential for development of resistance by Cryptosporidium parvum or Giardia lamblia to nitazoxanide has not been examined. **Susceptibility Tests:** For protozoa such as Cryptosporidium parvum and Giardia lamblia, standardized tests for use in clinical microbiology laboratories are not available.

INDICATIONS AND USAGE:
Diarrhea caused by Giardia lamblia or Cryptosporidium parvum: NT-TOX Oral Suspension (patients 1 year of age and older) and NT-TOX Tablets (patients 12 years and older) are indicated for the treatment of diarrhea caused by Giardia lamblia or Cryptosporidium parvum. NT-TOX Oral Suspension and NT-TOX Tablets have not been shown to be superior to placebo for the treatment of diarrhea caused by Cryptosporidium parvum in HIV-infected or immunodeficient patients.

CONTRAINDICATIONS: NT-TOX Tablets and NT-TOX Oral Suspension are contraindicated in patients with a prior hypersensitivity to nitazoxanide or any other ingredient in the formulations.

PRECAUTIONS: General: The pharmacokinetics of nitazoxanide in patients with compromised renal or hepatic function have not been studied. Therefore, nitazoxanide must be administered with caution to patients with hepatic and biliary disease, to patients with renal disease and to patients with combined renal and hepatic disease.
Information for Patients: Nitazoxanide Tablets and Nitazoxanide Oral Suspension should be taken with food.
Drug Interactions: Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur (e.g., warfarin). In vitro metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes. Although no drug-drug interaction studies have been conducted in vivo, it is expected that no significant interaction would occur when nitazoxanide is co-administered with drugs that either are metabolized by or inhibit cytochrome P450 enzymes. Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term carcinogenicity studies have not been conducted. Nitazoxanide was not genotoxic in the Chinese hamster ovary (CHO) cell chromosomal aberration assay or the mouse micronucleus assay. Nitazoxanide was genotoxic in one tester strain (TA 100) in the Ames bacterial mutation assay. Nitazoxanide did not adversely affect male or female fertility in the rat at 2400 mg/kg/day (approximately 20 times the clinical adult dose adjusted for body surface area).
Pregnancy: Teratogenic Effects
Pregnancy Category B: Reproduction studies have been performed at doses up to 3200 mg/kg/day in rats (approximately 26 times the clinical adult dose adjusted for body surface area) and 100 mg/kg/day in rabbits (approximately 2 times the clinical adult dose adjusted for surface area) and have revealed no evidence of impaired fertility or

harm to the fetus due to nitazoxanide. There are, however, no adequate and well-controlled studies in pregnant women. **Nursing Mothers:** It is not known whether nitazoxanide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nitazoxanide is administered to a nursing woman. **Pediatric Use:** A single Nitazoxanide Tablet contains a greater amount of Nitazoxanide than is recommended for pediatric dosing and should therefore not be used in pediatric patients 11 years or younger. Nitazoxanide For Oral Suspension should be used for dosing Nitazoxanide in pediatric patients. Safety and effectiveness of Nitazoxanide Oral Suspension in pediatric patients less than one year of age have not been studied. **Geriatric Use:** Clinical studies of Nitazoxanide Tablets and Nitazoxanide Oral Suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Nitazoxanide Tablets and Nitazoxanide Oral Suspension. As stated in the section, this therapy must be administered with caution to patients with renal and or hepatic impairment. **HIV-Infected or Immunodeficient Patients:** Nitazoxanide Tablets and Nitazoxanide Oral Suspension have not been studied for the treatment of diarrhea caused by Giardia lamblia in HIV-infected or immunodeficient patients. Nitazoxanide Tablets and Nitazoxanide Oral Suspension have not been shown to be superior to placebo for the treatment of diarrhea caused by Cryptosporidium parvum in HIV-infected or immunodeficient patients.

ADVERSE REACTIONS: Nitazoxanide Tablets: In controlled and uncontrolled clinical studies of 1,657 HIV-uninfected patients age 12 years and older who received various dosage regimens of Nitazoxanide Tablets, the most common adverse events reported regardless of causality assessment were: abdominal pain (6.6%), diarrhea (4.2%), headache (3.1%) and nausea (3.0%). In placebo-controlled clinical trials using the recommended dose, the rates of occurrence of these events did not differ significantly from those of the placebo. In placebo-controlled trials of HIV-uninfected patients age 12 years and older who received Nitazoxanide Tablets for the treatment of diarrhea caused by Giardia lamblia or Cryptosporidium parvum, less than 1% of patients discontinued therapy because of an adverse event. Adverse events occurring in less than 1% of the patients age 12 years and older participating in clinical trials of Nitazoxanide Tablets are listed below:

Body as a Whole: Asthenia, fever, pain, allergic reaction, pelvic pain, back pain, chills, chills and fever, flu syndrome. **Nervous System:** dizziness, somnolence, insomnia, tremor, hypesthesia. **Digestive System:** vomiting, dyspepsia, anorexia, flatulence, constipation, dry mouth, thirst. **Urogenital System:** discolored urine, dysuria, amenorrhea, metrorrhagia, kidney pain, edema labia. **Metabolic & Nutrition:** Increased SGPT. **Hemic & Lymphatic Systems:** anemia, leukocytosis. **Skin:** rash, pruritus. **Special Senses:** eye discoloration, ear ache. **Respiratory System:** epistaxis, lung disease, pharyngitis. **Cardiovascular System:** tachycardia, syncope, hypertension. **Muscular System:** myalgia, leg cramps, spontaneous bone fracture. **Nitazoxanide Oral Suspension:** In controlled and uncontrolled clinical studies of 613 HIV-uninfected pediatric patients who received Nitazoxanide Oral Suspension, the most frequent adverse events reported regardless of causality assessment were: abdominal pain (7.8%), diarrhea (2.1%), vomiting (1.1%) and headache (1.1%). These were typically mild and transient in nature. None of the 613 pediatric patients discontinued therapy because of adverse events. Adverse events occurring in less than 1% of the pediatric patients participating in clinical trials of nitazoxanide Oral Suspension are listed below: **Digestive System:** nausea, anorexia, flatulence, appetite increase, enlarged salivary glands. **Body as a Whole:** fever, infection, malaise. **Metabolic & Nutrition:** increased creatinine, increased SGPT. **Skin:** pruritus, sweat. **Special Senses:** eye discoloration (pale yellow). **Respiratory System:** rhinitis. **Nervous System:** dizziness. **Urogenital System:** discolored urine. The adverse events seen in adult patients treated with Nitazoxanide Oral Suspension were similar to those observed in adult patients treated with Nitazoxanide Tablets.

OVERDOSAGE: Information on nitazoxanide overdosage is not available. In the event of overdose, gastric lavage may be appropriate soon after dry administration. Patients should be carefully observed and given symptomatic and supportive treatment.

DOSAGE & ADMINISTRATION:

For Adults

Disease	Dosage
Diarrhea caused by G.lamblia or C.parvum	1 Tablet (500mg) every 12 hours (b.i.d) for 3-days.

For Children

Disease	Age	Dosage
Diarrhea caused by G.lamblia or C.parvum	1 - 3 years	1 teaspoonful (100mg) every 12 hours (b.i.d) for 3-days.
	4 - 11 years	2 teaspoonful (200mg) every 12 hours (b.i.d) for 3-days.

*7.5mg/kg bid

DIRECTIONS FOR RECONSTITUTION

NT-TOX For Oral Suspension: Tap the bottle before reconstitution. To make suspension add some water invert bottle and shake well until all granules are dispersed. Then slowly add more water up to the mark. Use only cool boiled water. Reconstituted suspension should be used within 7 days.

INSTRUCTION: Dosage as directed by the physician. Store below 30°C. Protect from heat, light & moisture. Keep all medicine out of the reach of children.

SHAKE WELL BEFORE USE.

PRESENTATION: NT-TOX (Nitazoxanide) Tablets 500mg are available in ALU-PVC blister pack of 2x10's with leaflet. NT-TOX (Nitazoxanide) For Oral Suspension 100mg/5mL is availbale in pack size of 30mL HDPE bottle with leaflet. NT-TOX (Nitazoxanide) for Oral Suspension 100mg/5mL is availbale in pack size of 60ml HDPE bottle with leaflet.

سسپنشن تیار کرنے کیلئے: سسپنشن تیار کرنے سے پہلے بوتل کو اچھی طرح ہلائیں۔
ایسے ہوئے خشک پاؤڈر پر پانی کی تھوڑی مقدار شامل کریں اور بوتل کو اچھی طرح ہلائیں تاکہ تمام دوا اچھی طرح حل ہو جائے۔
پھر مزید پانی دیئے ہوئے نشان تک شامل کر دیں اور بوتل کو دوبارہ اچھی طرح ہلائیں۔
تیار شدہ سسپنشن ۷ دن کے اندر استعمال کر لیں۔
ہدایات: خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۳۰°C سے کم ستی گرمی سے بچائیں۔ روشنی، گرمی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔ استعمال سے پہلے بوتل کو اچھی طرح ہلائیں۔

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