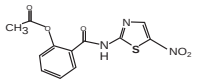
71 mm

220 mm

# Izato® Tablets / Suspension

( Nitazoxanide )

DESCRIPTION:
Nitazoxanide is a synthetic antiprotozoal agent for oral administration. 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 307.3. The structural formula is:



COMPOSITION:
**Izato®** 500mg Tablets
Each film coated tablet contains:
Nitazoxanide MS.....500mg

**Izato®** 100mg/5ml Suspension
Each 5ml of reconstituted suspension contains:
Nitazoxanide MS .....100mg

CLINICAL PHARMACOLOGY:
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

PHARMACOKINETICS:
Following oral administration of nitazoxanide tablets or oral suspension, maximum plasma concentrations of the active metabolites tizoxanide and tizoxanide glucuronide are observed within 1-4 hours. The parent nitazoxanide is not detected in plasma. Pharmacokinetic parameters of tizoxanide and tizoxanide glucuronide are shown in tables 1 and 2 below:

Table 1. Mean (±SD) plasma pharmacokinetic parameter values following administration of a single dose of one 500mg nitazoxanide tablet with food to subjects • 12 years of age

| Age | Tizoxanide | | | Tizoxanide Glucuronide | | |
|---|---|---|---|---|---|---|
| | $C_{max}$ (µg/ml) | *$T_{max}$ (hr) | $AUC_t$ (µg.hr/ml) | $C_{max}$ (µg/ml) | *$T_{max}$ (hr) | $AUC_t$ (µg.hr/ml) |
| 12-17 years | 9.1 (6.1) | 4.0 (1-4) | 39.5 (24.2) | 7.3 (1.9) | 4.0 (2-8) | 46.5 (18.2) |
| • 18 years | 10.6 (2.0) | 3.0 (2.4) | 41.9 (6.0) | 10.5 (1.4) | 4.5 (4-6) | 63.0 (12.3) |

*$T_{max}$ is given as a Mean (Range)

Table 2. Mean (± SD) plasma pharmacokinetic parameter values following administration of a single dose of nitazoxanide oral suspension with food to subjects • 1 year of age

| Age | Dose | Tizoxanide | | | Tizoxanide Glucuronide | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (µg/ml) | *$T_{max}$ (hr) | $AUC_{inf}$ (µg.hr/ml) | $C_{max}$ (µg/ml) | *$T_{max}$ (hr) | $AUC_{inf}$ (µg.hr/ml) |
| 1-3 years | 100mg | 3.11 (2.0) | 3.5 (2-4) | 11.7 (4.46) | 3.64 (1.16) | 4.0 (3-4) | 19.0 (5.03) |
| 4-11 years | 200mg | 3.00 (0.99) | 2.0 (1-4) | 13.5 (3.3) | 2.84 (0.97) | 4.0 (2-4) | 16.9 (5.00) |
| • 18 years | 500mg | 5.49 (2.06) | 2.5 (1-5) | 30.2 (12.3) | 3.21 (1.05) | 4.0 (2.5-6) | 22.8 (6.49) |

*$T_{max}$ is given as a Mean (Range)

Nitazoxanide oral suspension is not bioequivalent to nitazoxanide tablets. The relative bioavailability of the suspension compared to the tablet is 70%

Effect of Food: When nitazoxanide tablets are administered with food, the $AUC_t$ of tizoxanide and tizoxanide glucuronide in plasma is increased almost two-fold and the $C_{max}$ is increased by almost 50%. When nitazoxanide oral suspension is administered with food, the $AUC_t$ of tizoxanide and tizoxanide glucuronide increases by about 45-50% and the $C_{max}$ increases by •10%

Multiple dosing: Following oral administration of a single nitazoxanide tablet every 12 hours for 7 consecutive days, there was no significant accumulation of nitazoxanide metabolites tizoxanide or tizoxanide glucuronide detected in plasma

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 oral suspension in pediatric patients less than one year of age has not been studied

INDICATIONS:
Diarrhea caused by Giardia lamblia
Nitazoxanide oral suspension (patients 1 year of age and older) and nitazoxanide tablets (patients 12 years and older) are indicated for the treatment of diarrhea caused by Giardia lamblia

Diarrhea caused by Cryptosporidium parvum
Nitazoxanide for oral suspension is indicated for patients 1 through 11 years of age for the treatment of diarrhea caused by Cryptosporidium parvum

DOSAGE:

| Indication | Age | Dosage | Duration |
|---|---|---|---|
| Treatment of diarrhea caused by Giardia lamblia or Cryptosporidium parvum | 1-3 years | 5ml every 12 hours with food | 3 Days |
| | 4-11 years | 10ml every 12 hours with food | |
| | • 12 years | 1 tablet every 12 hours with food or 25ml suspension every 12 hours with food | |

OR
As directed by the physician

ADVERSE REACTIONS:
Adverse events reported with nitazoxanide tablets in less than 1% of the patients' age 12 years and older 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 of 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

Adverse events reported with nitazoxanide suspension in less than 1% of the pediatric patients' are listed below:

- *Digestive System:* Nausea, anorexia, flatulence, increased appetite, 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

Contraindications: Nitazoxanide tablets and 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

Pregnancy - Category B:
There are no adequate and well-controlled studies in pregnant women. Therefore, nitazoxanide should be used during pregnancy only if clearly needed

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 women

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

OVERDOSAGE:
Information on nitazoxanide overdosage is not available. In acute studies in rodents and dogs, the oral LD50 was higher than 10,000 mg/kg. Single oral doses of up to 4000mg nitazoxanide have been administered to healthy adult volunteers without significant adverse effects. In the event of overdose, gastric lavage may be appropriate soon after oral administration. Patients should be carefully observed and given symptomatic and supportive treatment

DIRECTIONS FOR RECONSTITUTION:
**Izato®** 100mg/5ml suspension (30ml)
Shake bottle to loosen the mass. Add one time completely filled provided cup (20ml) with freshly boiled cool water into bottle. Shake well to form uniform suspension

**Izato®** 100mg/5ml suspension (60ml)
Shake bottle to loosen the mass. Add one time completely filled provided cup (40ml) with freshly boiled cool water into bottle. Shake well to form uniform suspension

PRESENTATION:
**Izato®** 500mg tablets in pack of 20's
**Izato®** 100mg/5ml suspension in pack of 30ml
**Izato®** 100mg/5ml suspension in pack of 60ml

STABILITY:
See expiry on the pack

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine

The reconstituted suspension should be kept at 8 to 15°C, so that potency of the product remains stable and be used within 7 days

## ازیٹو® ٹیبلٹ / سسپینشن

(نیٹازوکسانائیڈ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
ہدایات: بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی
تیار شدہ سسپینشن کو ۸ سے ۱۵ ڈگری سینٹی گریڈ پر رکھیں
تاکہ دوا کی تاثیر برقرار رہے اور ۷ یوم کے اندر استعمال کریں

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
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