Alinia®
(nitazoxanide) Tablets
(nitazoxanide) for Oral Suspension

DESCRIPTION
Alinia Tablets and Alinia 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-acetylthiazolyl-5H-nitro-2-hiazolone. The molecular formula is C9H7N4O3S and the molecular weight is 307.3. The chemical is:

CH3
N
N
H
OO
O
CH3
NO2

Alinia Tablets contain 500 mg of nitazoxanide and the following inactive ingredients: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycolate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, FD&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake.

Alinia for Oral Suspension, after reconstitution, contains 100 mg nitazoxanide per 5 mL and the following inactive ingredients: sodium citrate dihydrate, acacia gum, sugar syrup, FD&C Red #40 and natural strawberry flavoring.

CLINICAL PHARMACOLOGY
Absorption: Following oral administration of Alinia Tablets or Oral Suspension, maximal plasma concentrations of the active metabolites tizoxanide and tizoxanide glucuronide are observed within 1 hour. 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 parameters following administration of a single dose of one 500 mg Alinia Tablet with food to subjects 2–12 years of age

<table>
<thead>
<tr>
<th>Tizoxanide</th>
<th>Tizoxanide glucuronide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (µg/mL)</td>
</tr>
<tr>
<td>12–17 years</td>
<td>9.1 (8.1)</td>
</tr>
<tr>
<td>≥18 years</td>
<td>10.9 (2.9)</td>
</tr>
</tbody>
</table>

Tmax is given as a Mean (Range)

Alinia for Oral Suspension is not bioequivalent to Alinia Tablets. The relative bioavailability of the suspension compared to the oral tablets was 70%.

Effect of Food: When Alinia 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 Alinia for Oral Suspension was administered with food, the AUC of tizoxanide and tizoxanide glucuronide increased by about 45-50% and the Cmax increased by 10%.

Table 2. Mean (SD) plasma pharmacokinetic parameters following administration of a single dose of Alinia for Oral Suspension with food to subjects 2–11 year of age

<table>
<thead>
<tr>
<th>Tizoxanide</th>
<th>Tizoxanide glucuronide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (µg/mL)</td>
</tr>
<tr>
<td>1-3 years</td>
<td>3.1 (2.0)</td>
</tr>
<tr>
<td>4-11 years</td>
<td>3.0 (0.98)</td>
</tr>
<tr>
<td>≥12 years</td>
<td>5.49 (2.06)</td>
</tr>
</tbody>
</table>

Tmax is given as a Mean (Range)

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
Diarhoea caused by Giardia lamblia or Cryptosporidium parvum: Alinia for Oral Suspension (patients 1 year of age and older) and Alinia Tablets (patients 12 years and older) are indicated for the treatment of diarhoea caused by Giardia lamblia or Cryptosporidium parvum.

Alinia for Oral Suspension and Alinia Tablets have not been shown to be superior to placebo for the treatment of diarrhoea caused by Cryptosporidium parvum in HIV-infected or immunodeficient patients (see CLINICAL STUDIES).

CONTRAINDICATIONS
Alinia Tablets and Alinia for 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
Alinia Tablets and Alinia for Oral Suspension should be taken with food.

Diabetic patients and caregivers should be aware that the oral suspension contains 1.48 grams of sucrose per 5 mL.

Drug Interactions
Tizoxanide is highly bound to plasma protein (>98%). 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 vivo 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 Alinia 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. Alinia for Oral Suspension should be used for dosing nitazoxanide in pediatric patients (See DOSAGE AND ADMINISTRATION).

Safety and effectiveness of Alinia for Oral Suspension in pediatric patients less than one year of age have not been studied.

Geriatric Use
Clinical studies of Alinia Tablets and Alinia for 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 Alinia Tablets and Alinia for Oral Suspension. As stated in the PRECAUTIONS section, this therapy must be administered with caution to patients with renal and or hepatic impairment.

HIV-infected or Immunodeficient Patients
Alinia Tablets and Alinia for Oral Suspension have not been studied for the treatment of diarrhoea caused by Giardia lamblia in HIV-infected or immunodeficient patients. Alinia Tablets and Alinia for Oral Suspension have not been shown to be superior to placebo for the treatment of diarrhoea caused by Cryptosporidium parvum in HIV-infected or immunodeficient patients (see CLINICAL STUDIES).

ADVERSE REACTIONS
Alinia Tablets: In controlled and uncontrolled clinical studies of 1,657 HIV-uninfected patients age 12 years and older who received various dosage regimens of Alinia Tablets, the most common adverse events reported regardless of causality assessment were abdominal pain (8.5%), diarrhoea (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 Alinia Tablets for the treatment of diarrhoea 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 Alinia 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, hypotension.

Digestive System: vomiting, dyspepsia, anorexia, flatulence, constipation, dry mouth, thirst.


Metabolic & Nutrition: increased SGPT.

Hemic & Lymphatic Systems: anaemia, leukocytosis.

Skin: rash, pruritus.

Special Senses: eye dislocation, ear ache.

Respiratory System: epistaxis, lung disease, pharyngitis.
Clinical response was evaluated 7 to 10 days following initiation of treatment with a 'well' response defined as 'no symptoms, no watery stools and no more than 2 soft stools within the past 24 hours.' Some patients with 'well' clinical responses had Cryptosporidium oocysts in their stool samples 4 to 7 days following the end of treatment. The relevance of stool examination results in these patients is unknown. Patients should be managed based on clinical response to treatment.

Diarrhea caused by Cryptosporidium parvum in pediatric patients 1 through 11 years of age:
In two double-blind, controlled studies in pediatric patients with diarrhea caused by Cryptosporidium parvum, a three-day course of treatment with nitazoxanide (100 mg BID in pediatric patients ages 12-47 months, 200 mg BID in pediatric patients ages 4 through 11 years) was compared with a placebo tablet for 3 days. A study conducted in Egypt in pedi

Clinical studies of nitazoxanide tablets conducted in Egypt in adults and adolescents with diarrhea caused by Cryptosporidium parvum: One study was conducted in Egypt in adults and adolescents with diarrhea caused by Cryptosporidium parvum. A second study was conducted in Egypt in pediatric patients ages 4 through 7 days following the end of treatment. The relevance of stool examination results in these patients is unknown. Patients should be managed based on clinical response to treatment.

Diarrhea caused by Cryptosporidium parvum in AIDS patients: A double-blind, placebo-controlled study did not produce clinical cure rates that were significantly different from the placebo group in hospitalized, severely malnourished pediatric patients with acquired immune deficiency syndrome (AIDS) in Zambia. In this study, the pediatric patients received a three day course of nitazoxanide suspension (100 mg BID in pediatric patients ages 12-47 months, 200 mg BID in pediatric patients ages 4 through 11 years) and were evaluated for response four days after the end of treatment.