

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-498**

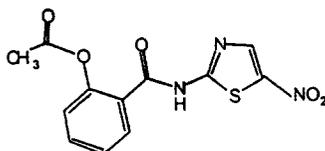
**Final Printed Labeling**

## PRESCRIBING INFORMATION

### Alinia™ (nitazoxanide) for Oral Suspension

#### DESCRIPTION

Alinia™ for Oral Suspension contains 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<sub>12</sub>H<sub>9</sub>N<sub>3</sub>O<sub>5</sub>S and the molecular weight is 307.3. The structural formula is:



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

#### CLINICAL PHARMACOLOGY

**Absorption:** Following oral administration of Alinia for 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 Table 1 below.

Table 1. Mean ( $\pm$  SD) plasma pharmacokinetic parameter values following administration of a single dose of Alinia for Oral Suspension with food to pediatric subjects

Age	Dose	Tizoxanide			Tizoxanide glucuronide		
		C <sub>max</sub> ( $\mu$ g/mL)	T <sub>max</sub> (hr)	AUC <sub>inf</sub> ( $\mu$ g·hr/mL)	C <sub>max</sub> ( $\mu$ g/mL)	T <sub>max</sub> (hr)	AUC <sub>inf</sub> ( $\mu$ g·hr/mL)
12-47 months	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)

\* Dose: 100 mg/5 mL nitazoxanide, 200 mg/10 mL nitazoxanide

\*\*T<sub>max</sub> is given as Mean (Range)

No studies have been conducted to determine if the pharmacokinetics of tizoxanide and tizoxanide glucuronide differ in fasted versus fed subjects following administration of Alinia for Oral Suspension.

**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.

**Elimination:** Tizoxanide is excreted in the urine, bile and feces, and tizoxanide glucuronide is excreted in urine and bile.

### 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.

**Pediatric Patients:** The pharmacokinetics of nitazoxanide 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* and *in vivo*

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*.

Alinia for Oral Suspension is effective in pediatric patients with *Cryptosporidium parvum* or *Giardia lamblia* infection (see INDICATIONS AND USAGE and CLINICAL STUDIES).

#### 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

Alinia for Oral Suspension is indicated for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in pediatric patients 1 through 11 years of age. Safety and effectiveness of Alinia for Oral Suspension have not been established in HIV positive patients or patients with immunodeficiency. (See CLINICAL STUDIES). Safety and effectiveness of Alinia for Oral Suspension in pediatric patients less than one year of age, pediatric patients greater than 11 years of age and adults have not been studied.

### CONTRAINDICATIONS

Nitazoxanide is contraindicated in patients with a prior hypersensitivity to nitazoxanide.

### 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 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 (>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.

No interactions with other medicinal products have been reported by patients using nitazoxanide. However, no clinical studies have been conducted to specifically exclude the possibility of interactions between nitazoxanide and other medicinal products.

### **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 mutagenicity assay.

Nitazoxanide did not adversely affect male or female fertility in the rat at 2400 mg/kg/day (approximately 66 times the recommended dose for patients 11 years of age, 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 48 times the clinical dose adjusted for body surface area) and 100 mg/kg/day in rabbits (approximately 3 times the clinical dose adjusted for body 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**

Safety and effectiveness of Alinia for Oral Suspension in pediatric patients less than one year of age or greater than 11 years of age have not been studied.

### **Adults and Geriatrics**

Safety and effectiveness of Alinia for Oral Suspension in adult and geriatric patients have not been studied.

### **HIV Positive Patients**

Safety and effectiveness of Alinia for Oral Suspension in HIV positive patients have not been established.

### **Immunodeficient Patients**

Safety and effectiveness of Alinia for Oral Suspension in immunodeficient patients have not been established.

### **ADVERSE REACTIONS**

In controlled and uncontrolled clinical studies of 613 HIV-negative pediatric patients who received Alinia for 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. In placebo-controlled clinical trials, the rates of occurrence of these events did not differ significantly from those of the placebo. None of the 613 pediatric patients discontinued therapy because of adverse events.

Adverse events occurring in less than 1% of the patients participating in clinical trials 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.

#### OVERDOSAGE

Information on nitazoxanide overdosage is not available. In acute studies in rodents and dogs, the oral LD<sub>50</sub> was higher than 10,000 mg/kg. Single oral doses of up to 4000 mg nitazoxanide in a tablet formulation 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.

#### DOSAGE & ADMINISTRATION

Age 12-47 months: 5 ml (100 mg nitazoxanide) every 12 hours for 3 days.

Age 4-11 years: 10 mL (200 mg nitazoxanide) every 12 hours for 3 days.

The oral suspension should be taken with food.

#### DIRECTIONS FOR MIXING ALINIA FOR ORAL SUSPENSION

Prepare a suspension at time of dispensing as follows: The amount of water required for preparation of the suspension is 48 mL. Tap bottle until all powder flows freely. Add approximately one-half of the total amount of water required for reconstitution and shake vigorously to suspend powder. Add remainder of water and again shake vigorously.

The container should be kept tightly closed, and the suspension should be shaken well before each administration. The suspension may be stored for 7 days, after which any unused portion must be discarded.

#### HOW SUPPLIED

Alinia for Oral Suspension is a pink-colored powder formulation that, when reconstituted as directed, contains 100 mg nitazoxanide/5 mL. The reconstituted suspension has a pink color and strawberry flavor. Alinia for Oral Suspension is available as:

60 mL bottle      NDC 67546-212-21

**Storage and Stability:** Store the unsuspended powder and the reconstituted oral suspension at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

#### CLINICAL STUDIES

##### *Cryptosporidium parvum*

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. One study was conducted in Egypt in outpatients ages 1 through 11 years with diarrhea caused by *C. parvum*. Another study was conducted in Zambia in malnourished pediatric patients admitted to the hospital with diarrhea caused by *C. parvum*. Clinical response was evaluated 3 to 7 days post-therapy with a 'well' response defined as 'no symptoms, no watery stools and no more than 2 soft stools with no hematochezia

within the past 24 hours' or 'no symptoms and no unformed stools within the past 48 hours.' The following clinical response rates were obtained:

**Pediatric patients with Diarrhea Caused by *Cryptosporidium parvum***  
**Clinical Response Rates 3 to 7 Days Post-therapy, Intent-to-Treat Analyses**  
 % (Number of Successes/Total)

Population	Nitazoxanide*	Placebo
Outpatient Study, age 1 to 11 years	88% (21/24)	38% (9/24)
Inpatient Study, Malnourished†, age 12-35 months	56% (14/25)	23% (5/22)

\* Clinical response rates statistically significantly higher compared to placebo.

† 60% considered severely underweight, 19% moderately underweight, 17% mild underweight.

Another double-blind, placebo-controlled study was conducted in hospitalized, severely malnourished pediatric patients with acquired immune deficiency syndrome (AIDS) in Zambia. In this study, 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) did not produce clinical cure rates that were significantly different from the placebo control.

*Giardia lamblia*

In a randomized, controlled study conducted in Peru in 110 pediatric patients with diarrhea caused by *Giardia lamblia*, a three-day course of treatment with nitazoxanide (100 mg BID in pediatric patients ages 24-47 months, 200 mg BID in pediatric patients ages 4 through 11 years) was compared to a five-day course of treatment with metronidazole (125 mg BID in pediatric patients ages 2 through 5 years, 250 mg BID in pediatric patients ages 6 through 11 years). 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 with no hematochezia within the past 24 hours' or 'no symptoms and no unformed stools within the past 48 hours.' The following clinical cure rates were obtained:

**Pediatric patients with Diarrhea Caused by *Giardia lamblia***  
**Clinical Response Rates 7 to 10 Days Following Initiation of Therapy**  
**Intent-to-Treat and Per Protocol Analyses**  
 % (Number of Successes/Total )  
 [95% Confidence Interval]

Population	Nitazoxanide (3 days)	Metronidazole (5 days)	95% CI Diff <sup>§</sup>
Intent-to-treat analysis <sup>†</sup>	85% (47/55)	80% (44/55)	[-9%, 20%]
Per protocol analysis <sup>†</sup>	90% (43/48)	83% (39/47)	[-8%, 21%]

<sup>†</sup> Intent-to-treat analysis includes all patients randomized with patients not completing the study treated as failures.

<sup>†</sup> Per protocol analysis includes only patients who took all of their medication and completed the study. Seven patients in each treatment group missed at least one dose of medication and one in the metronidazole treatment group was lost to follow-up.

<sup>§</sup> 95% Confidence Interval on the difference in response rates (nitazoxanide-metronidazole).

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Rx Only

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US Patents No. 5,578,621; 6,020,353; 5,968,961; 5,387,598; 6,117,894; 5,856,348; 5,859,138; 5,886,013;  
5,965,590.