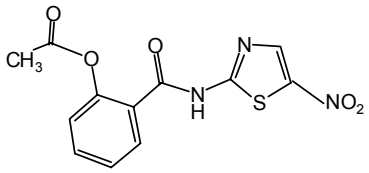
DRAFT PRESCRIBING INFORMATION

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-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:



Alinia Tablets contain 500 mg of nitazoxanide and the following inactive ingredients: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycollate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, talc, 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 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 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 500 mg Alinia Tablet with food to subjects ≥12 years of age

	Tizoxanide			Tizoxanide glucuronide		
Age	C_{max} (µg/mL)	T_{max}* (hr)	AUC_τ (µg•hr/mL)	C_{max} (µg/mL)	T_{max}* (hr)	AUC_τ (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 Alinia for Oral Suspension with food to subjects 1 through 11 years of age

		Tizoxanide			Tizoxanide glucuronide		
Age	Dose	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)

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

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

Effect of Food: When Alinia 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 Alinia for Oral Suspension was administered with food, the AUC_t of tizoxanide and tizoxanide glucuronide increased by about 45-50% and the C_{max} increased by ≤10%.

Alinia Tablets and for Oral Suspension were administered with food in clinical trials and hence they are recommended to be administered with food (see **DOSAGE AND ADMINISTRATION**).

Multiple dosing: Following oral administration of a single Alinia 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 Alinia Tablets in pediatric patients less than 12 years of age has not been studied. The pharmacokinetics of nitazoxanide following administration of Alinia for 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:*
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 diarrhea caused by *Giardia lamblia*.

Diarrhea caused by *Cryptosporidium parvum:*
Alinia for Oral Suspension is indicated for patients 1 through 11 years of age for the treatment of diarrhea caused by *Cryptosporidium parvum*.

Alinia for Oral Suspension and Alinia 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 (see **CLINICAL STUDIES**).

The safety and effectiveness of Alinia for Oral Suspension or Alinia Tablets for the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years of age and older have not been established.

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 (>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 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.

Geriatrics
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 diarrhea 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 diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients (see **CLINICAL STUDIES**).

ADVERSE REACTIONS
Alinia Tablets: In controlled and uncontrolled clinical studies of 1,628 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 (6.7%), diarrhea (4.3%),

headache (3.1%) and nausea (3.1%). 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 diarrhea caused by *Giardia lamblia*, approximately 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, 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.

Alinia for Oral Suspension: In controlled and uncontrolled clinical studies of 613 HIV-uninfected 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 pediatric patients participating in clinical trials of Alinia for 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 Alinia for Oral Suspension were similar to those observed in adult patients treated with Alinia Tablets.

OVERDOSAGE
Information on nitazoxanide overdosage is not available. In acute studies in rodents and dogs, the oral LD_{50} was higher than 10,000 mg/kg. Single oral doses of up to 4000 mg 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.

DOSAGE & ADMINISTRATION

Indication	Age	Dosage	Duration

Treatment of diarrhea caused by *Giardia lamblia*	1-3 years	5 mL of Alinia for Oral Suspension (100 mg nitazoxanide) every 12 hours with food	3 days
	4-11 years	10 mL of Alinia for Oral Suspension (200 mg nitazoxanide) every 12 hours with food	
	≥12 years	1 Alinia Tablet (500 mg nitazoxanide) every 12 hours with food or 25 mL of Alinia for Oral Suspension (500 mg nitazoxanide) every 12 hours with food	
Treatment of diarrhea caused by *Cryptosporidium parvum*	1-3 years	5 mL of Alinia for Oral Suspension (100 mg nitazoxanide) every 12 hours with food	3 days
	4-11 years	10 mL of Alinia for Oral Suspension (200 mg nitazoxanide) every 12 hours with food	

Safety and effectiveness of Alinia for Oral Suspension and Alinia Tablets for the treatment of diarrhea caused by *Cryptosporidium parvum* in patients 12 years and older have not been established.

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 Tablets and Alinia for Oral Suspension have not been studied for the treatment of *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 diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients (see **CLINICAL STUDIES**).

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 Tablets are round, yellow, film-coated tablets debossed with ALINIA on one side and 500 on the other side. Each tablet contains 500 mg of nitazoxanide. The tablets are packaged in HDPE bottles of 60 tablets and blister cards of 6 tablets.

Bottles of 60	NDC 67546-111-11
Boxes of 3 blister cards (Alinia 3-Day Therapy Packs™)	NDC 67546-111-32

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:

Bottles of 60 mL NDC 67546-212-21

Storage and Stability: Store the tablets, 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

Diarrhea caused by *Giardia lamblia* in adults and adolescents 12 years of age or older:

In a double-blind, controlled study (Study 1) conducted in Peru and Egypt in adults and adolescents with diarrhea caused by *Giardia lamblia*, a three-day course of treatment with Alinia Tablets administered 500 mg BID was compared with a placebo tablet and Alinia for Oral Suspension administered 500mg/25mL of suspension BID for 3 days. A second double-blind, controlled study (Study 2) conducted in Egypt in adults and adolescents with diarrhea caused by *Giardia lamblia* compared Alinia Tablets administered 500 mg BID for 3 days to a placebo. For both of these studies, clinical response was evaluated 4 to 7 days following the end of treatment. A clinical response of 'well' was 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:

Adult and Adolescent Patients with Diarrhea Caused by *Giardia lamblia*
Clinical Response Rates* 4 to 7 Days Post-therapy
% (Number of Successes/Total)

	Alinia Tablets	Alinia for Oral Suspension	Placebo Tablets
Study 1	85% (46/54) ¶ §	83% (45/54) ¶ §	44% (12/27)
Study 2	100% (8/8)	-	30% (3/10)

* Includes all patients randomized with *Giardia lamblia* as the sole pathogen. Patients failing to complete the studies were treated as failures.

¶ Clinical response rates statistically significantly higher when compared to placebo.

§ The 95% confidence interval of the difference in response rates for the tablet and suspension is (-14%, 17%).

Some of the patients with 'well' clinical responses had *Giardia lamblia* cysts 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 upon clinical response to treatment.

Diarrhea caused by *Giardia lamblia* in pediatric patients 1 through 11 years of age:

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§
Intent-to-treat analysis†	85% (47/55)	80% (44/55)	[-9%, 20%]

Per protocol analysis¶	90% (43/48)	83% (39/47)	[-8%, 21%]

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

¶ 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.

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

Some of the patients with 'well' clinical responses had *Giardia lamblia* cysts 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 upon 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. 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 - 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.

Some of the patients with 'well' clinical responses had *Cryptosporidium* oocysts in their stool samples 3 to 7 days following the end of treatment. The relevance of stool examination results in these patients is unknown. Patients should be managed based upon clinical response to treatment.

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.

Rx Only

US Patents No. 5,578,621; 6,020,353; 5,968,961; 5,387,598; 6,117,894; 5,965,590.

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