

# Nitazoxanide: A New Thiazolide Antiparasitic Agent

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**Nitazoxanide is a new thiazolide antiparasitic agent that shows excellent in vitro activity against a wide variety of protozoa and helminths. It is given by the oral route with good bioavailability and is well tolerated, with primarily mild gastrointestinal side effects. At present, there are no documented drug-drug interactions. Nitazoxanide has been licensed for the treatment of *Giardia intestinalis*-induced diarrhea in patients  $\geq 1$  year of age and *Cryptosporidium*-induced diarrhea in children aged 1–11 years. At present, it is pending licensure for treatment of infection due to *Cryptosporidium* species in adults and for use in treating immunocompromised hosts. It represents an important addition to the antiparasitic arsenal.**

Intestinal parasitic infections rank among the most significant causes of morbidity and mortality in the world today. Nevertheless, it has been >30 years since the introduction of any new innovative treatment and, for some pathogens (including *Cryptosporidium*), there is currently no accepted specific therapy [1]. Nitazoxanide, 2-acetyloxy-*N*-(5-nitro-2-thiazolyl) benzamide (Alinia; Romark Laboratories), is a new nitrothiazole benzamide compound notable for its activity in treating both intestinal protozoal and helminthic infections. It was first described in 1975 by Jean Francois Rossignol and was initially developed as a veterinary antihelminthic with activity against intestinal nematodes, cestodes, and liver trematodes [2]. In humans, nitazoxanide has been reported to be effective against a broad range of parasites, including *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Trichomonas vaginalis*, *Vitiforma corneae*, *Encephalitozoon intestinalis*, *Isospora belli*, *Blasitocystis hominis*, *Balantidium coli*, *Enterocytozoon bieneusi*, *Ascaris lumbricoides*, *Trichuris trichura*, *Taenia saginata*, *Hymenolepis nana*, and *Fasciola hepatica* [3–9]. In vitro studies have also shown antimicrobial activity against numerous gram-positive and gram-negative anaerobic bacteria, specifically *Bacteroides* species, *Clostridium* species, and *Helicobacter pylori*, and against aerobic gram-positive bacteria [10, 11].

Since 1996, nitazoxanide has been marketed in most of Latin

America and has been studied worldwide. The US Food and Drug Administration (FDA) approved oral suspension nitazoxanide in December of 2002 for the treatment of diarrhea caused by *Cryptosporidium* species and *Giardia intestinalis* in pediatric patients 1–11 years of age, and in July 2004, nitazoxanide was approved for treatment of diarrhea caused by *G. intestinalis* in adults. It is the first and only US FDA-approved drug for treatment of *Cryptosporidium* infection and is the first new drug approved for treatment of *Giardia* infection in >40 years.

## IN VITRO ACTIVITY

Studies of protozoa and anaerobic bacteria have shown that nitazoxanide inhibits pyruvate-ferredoxin oxidoreductase (PFOR), an enzyme essential to anaerobic energy metabolism [12]. However, interference with the PFOR enzyme-dependent electron transfer reaction may not be the only pathway by which nitazoxanide exhibits antiprotozoal activity, and the mechanism of nitazoxanide's activity against helminths is unknown.

Nitazoxanide has demonstrated in vitro activity against *C. parvum* and *G. intestinalis*. It has been shown to inhibit the growth of sporozoites of *C. parvum* on its own [13, 14], and has also demonstrated combined in vitro activity with both azithromycin and rifampin, suppressing growth of *C. parvum* by 83.9% and 79.8%, respectively, compared with 56.1% when used alone [15]. Similarly, in vitro studies of nitazoxanide and its derivative, tizoxanide, have shown greater efficacy than metronidazole against *G. intestinalis* [16]. Specifically, tizoxanide was demonstrated to be 8 times more active than metronidazole against metronidazole-susceptible isolates of *G. intestinalis* and twice as active against resistant isolates [17].

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Nitazoxanide has also shown broad in vitro activity against numerous other parasitic and microbial pathogens, including *E. intestinalis* [18], *V. corneae* [18], *E. histolytica* [16], *T. vaginalis* [16], *B. hominis* [19], *Echinococcus multilocularis* [20], *Echinococcus granulosus* [21], and *F. hepatica* [22]. The antimicrobial properties of nitazoxanide and tizoxanide have been tested against 241 anaerobes, the majority of which were inhibited in vitro, with an MIC<sub>90</sub> between 0.06 mg/L and 4 mg/L [10]. Nitazoxanide has also shown in vitro and in vivo antimicrobial activity against *Clostridium difficile* [23] and both metronidazole-susceptible and metronidazole-resistant strains of *H. pylori* [11, 24].

## PHARMACOLOGY

Nitazoxanide is available in oral suspension at a dose of 100 mg per 5 mL or in tablet formulation at a dose of 500 mg. The oral suspension, when reconstituted with water, has a pink color and a strawberry flavor. The recommended dosage for children aged 12–47 months is 100 mg b.i.d. for 3 days, and for children aged 4–11 years, the recommended dosage is 200 mg b.i.d. for 3 days. The recommended adult dosage is 500 mg b.i.d. for 3 days. The bioavailability of nitazoxanide is nearly doubled by administration with food [25].

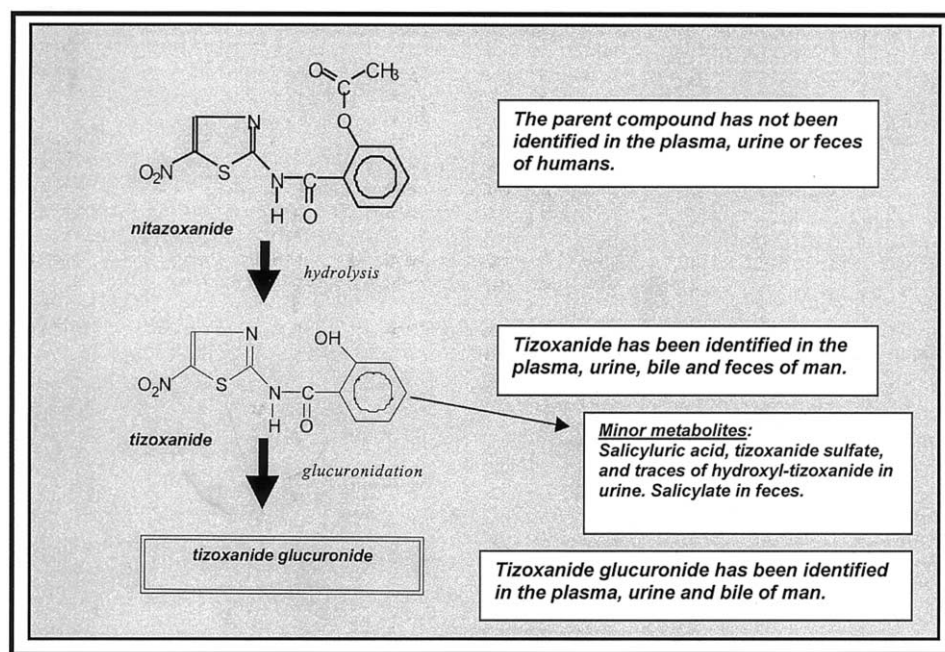
Studies of pharmacokinetics in humans have shown that nitazoxanide is absorbed from the gastrointestinal tract, with approximately one-third of the oral dose excreted in urine and two-thirds excreted in feces [26]. In blood, nitazoxanide is rapidly hydrolyzed by plasma esterases into its desacetyl deriv-

ative, tizoxanide (desacetyl-nitazoxanide) [27]. Tizoxanide is the active metabolite in vivo and the only measurable species in plasma. Following oral administration of nitazoxanide, a maximum tizoxanide plasma concentration of 2 mg/L is observed within 1–4 h [27]. Tizoxanide is extensively bound to plasma proteins (>99%), and its urinary elimination half-life is 7.3 h [27]. Tizoxanide then undergoes glucuronidation to form tizoxanide glucuronide (figure 1). The parent drug, nitazoxanide, is not detected in plasma, urine, bile, or feces. Tizoxanide is found in plasma, urine, bile, and feces, and tizoxanide glucuronide is found in plasma, urine, and bile [27].

Although in vitro metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P-450 enzymes, the pharmacokinetics of nitazoxanide in patients with compromised renal or hepatic function have not been studied, and nitazoxanide must be administered with caution to these patients [28]. In addition, the safety of nitazoxanide in pregnant or lactating women is unproven, because adequate studies have not yet been done.

## DRUG INTERACTIONS

At this time, no drug-drug interaction studies have been conducted with nitazoxanide in vivo. Because >99% of tizoxanide is bound to plasma proteins, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices. It is recommended to monitor the prothrombin time for patients who are concurrently taking warfarin and nitazoxanide.



**Figure 1.** Summary of nitazoxanide metabolism (published with permission of Romark Laboratories)

## SIDE EFFECTS

Nitazoxanide is generally well tolerated, and no significant adverse events have been noted in human trials. Adverse events have been mild and transient and principally related to the gastrointestinal tract, such as abdominal pain, diarrhea, and nausea. Adverse events occurring in <1% of more than 2000 HIV-uninfected patients participating in clinical trials included anorexia, flatulence, increased appetite, enlarged salivary glands, fever, infection, malaise, elevated creatinine levels, elevated levels of alanine aminotransferase in serum, pruritus, sweat, pale yellow sclerae, rhinitis, dizziness, and discolored urine [27]. In addition, there have been no significant changes in results of electrocardiography, vital signs, or hematologic, clinical chemistry, or urinalysis parameters in patients treated with nitazoxanide [29]. Nitazoxanide has been well tolerated up to the maximum dose of 4 g when taken with or without food, but the frequency of gastrointestinal side effects increases significantly with the dose level [25].

## CLINICAL USE

**Cryptosporidiosis.** Nitazoxanide was approved for use in treating *Cryptosporidium* infection in children aged 1–11 years on the basis of 2 double-blind, randomized, placebo-controlled clinical trials in Egypt and Zambia with 50 children in each trial [8, 30]. In each of these studies, patients had documented cryptosporidial diarrhea, and nitazoxanide was administered for 3 days. The patients were clinically evaluated 7–10 days after initiating treatment, and 2 posttreatment stool samples collected  $\geq 24$  h apart were examined for parasitological response. The results from the Egyptian clinical trial demonstrated that 80% of patients treated with nitazoxanide had resolved diarrhea and associated symptoms 7 days after initiation of therapy, compared with 41% of the placebo group. The median time from initiation of treatment to the passage of the last unformed stool was 3 days for patients treated with nitazoxanide, whereas 59% of the placebo group were still reporting diarrhea at the end of the follow-up period. Sixty-seven percent of patients treated with nitazoxanide did not produce *C. parvum* oocysts in either of the 2 posttreatment stool samples, compared with 22% of patients in the placebo group [8]. These data are further supported by an open-label Egyptian study involving 49 adults and children, which demonstrated a 67% rate of eradication of parasites 7–10 days after initiation of a 3-day course of nitazoxanide [31].

The randomized, placebo-controlled study from Zambia demonstrated that, among 25 malnourished HIV-negative children with cryptosporidiosis, a 3-day course of therapy led, not only to clinical and parasitological improvement, but also to improved survival. Diarrhea resolved in 14 (56%) of 25 HIV-seronegative children receiving nitazoxanide, compared with 5

(23%) of 22 receiving placebo, and *C. parvum* was eradicated from stool by day 10 after initiation of treatment in 52% of patients receiving nitazoxanide and 14% of patients receiving placebo. Treatment with nitazoxanide was suggested to improve survival, because by day 8 of treatment, 18% of children in the placebo group and none of the children in the nitazoxanide group had died [30].

**Giardiasis.** Nitazoxanide is approved for the treatment of infections due to *G. intestinalis* in patients  $\geq 1$  year of age. Two randomized controlled clinical trials, in Egypt and Peru, have demonstrated nitazoxanide's efficacy against placebo and its comparability with metronidazole and mebendazole in treating giardiasis in children. Open-label clinical studies in Mexico and Egypt evaluating nitazoxanide for treatment of mixed parasitic infections with protozoa and helminths have demonstrated eradication rates for *G. intestinalis* of 71%–94% with nitazoxanide treatment [3, 32].

In the prospective, randomized, double-blind, placebo-controlled study conducted in Egypt among 89 adults and adolescents with diarrhea caused by *G. intestinalis* and *E. histolytica* and/or *Entamoeba dispar*, 81% of patients treated with nitazoxanide resolved diarrhea within 7 days after initiation of treatment, compared with 40% of the placebo group. The median time to resolution of diarrhea was 3 days for the nitazoxanide treatment group, whereas 60% of the placebo group were still reporting diarrhea 7 days after treatment. The parasitological response rate for *G. intestinalis* from each of 2 stool samples collected between 7 and 10 days after initiation of treatment was 71% for patients taking nitazoxanide, compared with 0% for the placebo group [7].

Nevertheless, 2 randomized controlled trials and 1 observational study have demonstrated only equal efficacy between nitazoxanide and other antiparasitic drugs. One randomized controlled clinical trial among 110 children in Peru with documented giardiasis compared the activity of a 5-day course of metronidazole with that of a 3-day course of nitazoxanide. In an intention-to-treat analysis, 85% of the children treated with nitazoxanide had resolved their diarrhea at the follow-up examination, compared with 80% of those treated with metronidazole. In addition, only 71% of children in the nitazoxanide-treated group demonstrated a parasitological cure, compared with 75% of those treated with metronidazole [6]. Similarly, a double-blind controlled trial in Mexico involving 275 children that compared nitazoxanide with quinifamide and mebendazole in the treatment of helminthic infections and intestinal protozoa showed no statistically significant difference in rates of eradication of parasites between nitazoxanide and quinifamide, mebendazole, or both (64% vs. 57%) [33]. Again, equal efficacy was observed in an observational study involving 82 Mexican children; in this study, treatment with nitazoxanide resulted in clearing of *G. lamblia* cysts in 78% of patients, and treatment with mebendazole re-

**Table 1. Parasitological response rate of nitazoxanide in clinical studies of protozoan and helminthic infections.**

Parasite, study, group	No. of patients	Parasitological cure rate, no. (%) of patients	Clinical cure rate, no. (%) of patients
<b>Protozoa</b>			
<i>Cryptosporidium</i> species			
Abdel-Maboud [31]			
All	49	33 (67)	39 (80)
Adults	25	15 (60)	18 (72)
Children	24	18 (75)	21 (88)
Diaz [41]	NR	NR (100)	...
Rossignol [8]	49	33 (67)	39 (80)
Amadi <sup>a</sup> [30]			
HIV-seronegative	25	13 (52)	14 (56)
HIV-seropositive	25	4 (16)	2 (8)
Doumbo <sup>b</sup> (patients with stage 4 AIDS) [36]	12	7 (58)	...
Rossignol <sup>c</sup> [37]			
CD4 cell count >50/mm <sup>3</sup>			
500 mg b.i.d.	19	12 (63)	...
1 g b.i.d.	15	10 (67)	...
CD4 cell count ≤50/mm <sup>3a</sup>			
500 mg b.i.d.	5	2 (40)	...
1 g b.i.d.	5	1 (20)	...
<i>Giardia lamblia</i> , <i>Giardia intestinalis</i> , <i>Giardia duodenalis</i>			
Abaza [3]	139	130 (94)	...
Davila-Gutierrez <sup>d</sup> [33]	55	35 (64)	...
Diaz [41]	NR	NR (69)	...
Ortiz [6]	55	39 (71)	47 (85)
Rodriguez-Garcia [34]	41	32 (78)	...
Romero Cabello <sup>e</sup> [32]	87	62 (71)	...
Rossignol [7]	17	12 (71)	...
<i>Entamoeba histolytica/Entamoeba dispar</i>			
Abaza [3]	156	127 (81)	...
Davila-Gutierrez <sup>d</sup> [33]	47	40 (85)	...
Diaz [41]	NR	NR (96)	...
Romero Cabello <sup>e</sup> [32]	164	133 (81)	...
Rossignol [7]	36	25 (69)	...
<i>Blastocystis hominis</i>			
Diaz [41]	NR	NR (97)	...
Romero Cabello <sup>e</sup> [32]	10	10 (100)	...
<i>Isospora belli</i>			
Romero Cabello <sup>e</sup> [32]	2	2 (100)	...
<i>Balantidium coli</i>			
Abaza [3]	13	10 (77)	...
<i>Cyclospora cayetanensis</i>			
Diaz [41]	NR	NR (71)	...
<b>Helminths</b>			
<i>Ascaris lumbricoides</i>			
Abaza [3]	155	147 (95)	...
Davila-Gutierrez <sup>d</sup> [33]	42	29 (69)	...
Diaz [41]	NR	NR (100)	...
Ortiz [40]	28	25 (89)	...
Romero Cabello <sup>e</sup> [32]			
All	220	177 (80)	...
Light egg burden (<2000 eggs/g)	43	43 (100)	...
Moderate egg burden (2000–10,000 eggs/g)	144	118 (82)	...
Heavy egg burden (>10,000 eggs/g)	33	16 (48)	...

(continued)

**Table 1. (Continued.)**

Parasite, study, group	No. of patients	Parasitological cure rate, no. (%) of patients	Clinical cure rate, no. (%) of patients
<i>Trichuris trichiura</i>			
Abaza [3]	29	25 (86)	...
Davila-Gutierrez <sup>d</sup> [33]	22	18 (82)	...
Diaz [41]	NR	NR (100)	...
Ortiz [40]	18	16 (89)	...
Romero Cabello <sup>e</sup> [32]			
All	95	72 (76)	...
Light egg burden (<2000 eggs/g)	86	67 (78)	...
Moderate egg burden (2000–5000 eggs/g)	9	5 (56)	...
<i>Hymenolepis nana</i>			
Abaza [3]	62	53 (85)	...
Davila-Gutierrez <sup>d</sup> [33]	19	18 (95)	...
Diaz [41]	NR	NR (80)	...
Ortiz [40]	39	32 (82)	...
Romero Cabello <sup>e</sup> [32]			
All	180	168 (93)	...
Light egg burden (<2000 eggs/g)	130	126 (97)	...
Moderate egg burden (2000–5000 eggs/g)	50	42 (84)	...
<i>Taenia saginata</i>			
Romero Cabello <sup>e</sup> [32]	5	5 (100)	...
Rosignol <sup>f</sup> [4]	22	21 (95)	...
<i>Enterobius vermicularis</i>			
Abaza [3]	112	106 (95)	...
Diaz [41]	NR	NR (100)	...
Romero Cabello <sup>e</sup> [32]	5	4 (80)	...
<i>Ancylostoma duodenale</i>			
Abaza [3]	46	44 (96)	...
<i>Strongyloides stercoralis</i>			
Abaza [3]	36	34 (94)	...
<i>Fasciola hepatica</i>			
Favennec <sup>g</sup> [43]			
Adults	30	18 (60)	...
Children	35	14 (40)	...
Kabil <sup>h</sup> [42]	125	121 (97)	...
Rosignol <sup>i</sup> [9]	137	113 (82)	...

**NOTE.** All studies involve b.i.d. dosing of nitazoxanide for 3 days and 1–3 follow-up fecal examinations 7–10 days after initiation of treatment, unless otherwise indicated. NR, not reported.

<sup>a</sup> No difference compared with placebo.

<sup>b</sup> Treatment course lasted 7 days. Follow-up involved 2 posttreatment fecal examinations on day 7 and day 14 after initiation of treatment. Parasitological cure was defined as 2 negative results of fecal examination or a >95% reduction in oocyst shedding.

<sup>c</sup> Treatment course lasted 14 days. Follow-up involved 3 fecal examinations after treatment on days 15, 22, and 29 after initiation of treatment.

<sup>d</sup> Follow-up fecal examinations occurred 14 days after initiation of treatment.

<sup>e</sup> Parasitological response involves 6 negative posttreatment stool samples on days 6, 7, 8 ( $\pm 1$ ), 13, 14, and 15 ( $\pm 1$ ) after initiation of treatment.

<sup>f</sup> Treatment consisted of a single 25-mg/kg dose. Follow-up involved 3 posttreatment fecal examinations on days 30, 50, and 90 after initiation of treatment.

<sup>g</sup> Treatment course lasted 7 days. Follow-up involved 3 posttreatment fecal examinations between 30 and 90 days after initiation of treatment.

<sup>h</sup> Treatment course lasted 6 days. Follow-up involved 1 posttreatment fecal examination 30 days after initiation of treatment.

<sup>i</sup> Treatment course lasted 7 days. Follow-up involved 3 posttreatment fecal examinations on days 4, 6, and 30 after initiation of treatment.

sulted in clearing in 80.4% [34]. Nitazoxanide may have a role in treating metronidazole-resistant giardiasis, because a published case report and several in vitro studies have demonstrated its activity in this context [16, 17, 35].

## NONLICENSED USES

### Cryptosporidiosis in Patients with AIDS

At present, nitazoxanide is not licensed for use in treating immunodeficient persons with infections caused by *Cryptosporidium* species, although licensure is expected in the future (Romark Laboratories, personal communication). Clinical trials have taken place to determine the efficacy of nitazoxanide against *Cryptosporidium* infection in persons with AIDS. Ethical issues involved in performing placebo-controlled trials enrolling patients with AIDS-associated cryptosporidiosis have led to the use of historical controls and open-label trials to determine the efficacy of nitazoxanide in this population. To date, the results of these trials have been varied. Initial reports from a small open-label trial conducted in Africa and a double-blind, placebo-controlled trial in Mexico produced favorable results, particularly for patients with higher CD4<sup>+</sup> cell counts. In Mali, 12 patients with clinical stage 4 AIDS and documented cryptosporidiosis were evaluated. After receiving nitazoxanide for 7 days, 7 patients (58%) demonstrated eradication or reduction by >95% of *C. parvum* oocysts in feces, and 4 patients had complete resolution of diarrhea [36]. Nevertheless, the drug demonstrated greater efficacy in treating patients with lighter infections than in treating those with moderate to heavy infections. A double-blind, placebo-controlled crossover study in Mexico evaluated 66 patients with AIDS and cryptosporidiosis who were randomly assigned to receive nitazoxanide at 500 mg b.i.d. or 1000 mg b.i.d. or placebo for 14 days. This study demonstrated that, in patients with CD4<sup>+</sup> cell counts of >50 cells/mm<sup>3</sup>, both doses of nitazoxanide produced parasitological cure rates superior to the placebo responses (63%, 67%, and 25%, respectively), and 86% of patients who were parasitologically cured had complete resolution of diarrhea. In contrast, in patients with CD4<sup>+</sup> cell counts of ≤50 cells/mm<sup>3</sup>, there was no statistical difference between the treated groups and the placebo group at the doses used [37]. Similarly, in a Zambian study of HIV-seropositive children with cryptosporidiosis, a 3-day course of nitazoxanide did not show significant efficacy in clinical or parasitological response [30]. Preliminary analysis of a clinical trial in the United States involving 22 patients with AIDS and *Cryptosporidium* infection who were treated with nitazoxanide for 4 weeks revealed that 15 (68%) had a reduction in frequency of bowel movements, but only 4 patients lacked detectable oocysts in the stool [38, 39]. These studies suggest that a higher dose and/or extended duration of treatment may be required to achieve a sustained clinical and parasitological response in the immunocompromised population, yet addi-

tional multicenter clinical trial data are needed. Based on the results of a recently completed clinical trial in patients with AIDS, the recommended dosage and duration of treatment for immunodeficient patients with cryptosporidiosis is 1000 mg b.i.d. for 2–8 weeks (Romark Laboratories, personal communication).

### Helminthic Infections

**A. lumbricoides.** A randomized clinical study conducted in Peru evaluated the efficacy of a 3-day course of nitazoxanide, compared with a single 400-mg dose of albendazole, in the treatment of ascariasis in children aged 1–11 years and demonstrated comparable parasite egg–reduction rates between the 2 treatment arms (89% vs. 91%) [40]. Clinical studies in Mexico have shown parasite elimination rates ranging from 48% for heavy infections to 100% for light infections with *Ascaris* [32, 33, 41]. A multicenter clinical study conducted in Egypt and involving 546 patients who were treated with a 3-day course of nitazoxanide demonstrated 95% efficacy in eradication of *Ascaris* from stool 7 days after initiation of treatment [3].

**T. trichiura.** In the same Peruvian study [40], a 3-day course of nitazoxanide was demonstrated to have a higher cure rate (89% vs. 58%) and statistically significant egg reduction rate 21–30 days after treatment for trichuriasis in children aged 2–11 years, compared with a single 400-mg dose of albendazole. Similarly effective treatment with nitazoxanide has been seen in studies in Mexico and Egypt, in which rates of reduction of parasites ranged from 56% for moderate infections to 100% for light infections [3, 32, 33, 41].

**H. nana.** Initial clinical studies of nitazoxanide demonstrated efficacy against *H. nana* in a single oral dose of 50 mg/kg [4], and studies from Mexico and Egypt have shown parasite reduction rates ranging from 84% for moderate infections to 97% for light infections [3, 32, 33]. Nevertheless, in a clinical study comparing a 3-day course of nitazoxanide with a single 25-mg/kg dose of praziquantel for treatment of *H. nana* infection in Peruvian children, nitazoxanide was found to be less efficacious than praziquantel (82% cure rate vs. 96% cure rate), although this was not statistically significant [40].

**T. saginata.** The results of a clinical study have shown that a single 25-mg/kg dose of nitazoxanide was effective in eradicating *T. saginata* from stools of 21 of 22 patients who were followed-up for 90 days after treatment [4]. A Mexican study showed a 100% parasite eradication rate, although the sample size was small (5 cases) [32].

**F. hepatica.** At present, there is no currently licensed therapy available for chronic fascioliasis. An open-label clinical study of 125 Egyptian patients treated for 6 days with nitazoxanide demonstrated 97% clearance of *F. hepatica* eggs in the stool on day 30, as well as decreasing serological titers in 78% of patients [42]. A second report from Egypt in the treat-

ment of *F. hepatica* with nitazoxanide has demonstrated a slightly lower cure rate of 82.4% [9]. In northern Peru, a double-blind, placebo-controlled study of 50 adults and 50 children infected with *F. hepatica* demonstrated that a 7-day course of nitazoxanide produced a parasite elimination rate of 60% in adults and 40% in children 90 days after patient enrollment, compared with 13% in adults and 0% in children receiving placebo [43]. On the basis of these data, a 7-day course is recommended for treatment for *F. hepatica* [28].

**Other helminthic infections.** Other human helminthic infections for which nitazoxanide has shown activity in clinical trials include enterobiasis (80%–100% eradication) [3, 32, 41], ancylostomiasis (96%) [3], and strongyloidiasis (94%) [3].

### Protozoan Infections

Nitazoxanide has shown activity in clinical trials against numerous protozoan infections in addition to cryptosporidiosis and giardiasis. Five clinical studies from Egypt and Mexico have evaluated nitazoxanide's efficacy in treatment of *E. histolytica* and *E. dispar* and have found parasite eradication rates of 69%–96% [3, 7, 32, 33, 41]. Parasite eradication rates for *B. hominis* in clinical studies have ranged from 97% to 100% [32, 41]. One clinical study demonstrated a 100% eradication rate for *I. belli* in 2 cases [32]. Additionally, clinical studies have shown a 71% eradication rate for *C. cayetanensis* [41, 44] and a 77% eradication rate for *B. coli* based on 1 posttreatment fecal examination on day 7 after initiation of treatment [3]. Nitazoxanide has also demonstrated activity against microsporidiosis caused by *E. bienewisi* in patients with AIDS [45]. The parasitological response rates of nitazoxanide in clinical studies of protozoan and helminthic infections are summarized in table 1.

### SUMMARY

Nitazoxanide is a new nitrothiazole compound with broad-spectrum activity against numerous intestinal protozoa, helminths, and anaerobic bacteria. It is presently approved to treat infections due to *G. intestinalis* in children and adults and infections due to *Cryptosporidium* species in children. Approval for use in adults with *Cryptosporidium* infection and the immunocompromised population is on the horizon. Nitazoxanide is an important new addition to the antiparasitic pharmacopeia. The drug has few side effects and requires a short course of treatment. Nevertheless, a need remains for further studies of its molecular mechanisms of action, bioavailability, and drug interactions to learn whether it can be safely used in a variety of patient groups. Because the majority of parasitic infections occur in the developing world, further data about drug potency and stability are also needed to support its widespread use in this context. Similarly, clinical and pharmacological data on absorption, dosage, and duration of therapy in patients with AIDS and chronic cryptosporidiosis

are necessary. In view of its unique mechanism of action, nitazoxanide should be considered for further clinical evaluation in the treatment of parasitic infections (e.g., in combination with paromomycin or azithromycin for treatment of cryptosporidiosis and in combination with albendazole for treatment of intestinal helminth infections) and in reducing the emergence of metronidazole resistance, particularly with *Giardia* and *H. pylori*. Additional clinical trial data that would expand our knowledge of nitazoxanide's utility in these contexts is important. With these questions answered, nitazoxanide may represent a significant advance in the treatment of intestinal parasitic infections worldwide.

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