National PBM Drug Monograph
Nitazoxanide (Alinia®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

INTRODUCTION
Nitazoxanide (NTZ) oral suspension was approved in November 2002 for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia* in children aged 1-11 years. In July 2004, nitazoxanide was approved for the treatment of diarrhea caused by *Giardia lamblia* in patients ≥ 12 years old. Safety and efficacy have not been established in HIV positive patients or patients with immunodeficiency. Phase III clinical trials for the treatment of *Cryptosporidium*-induced diarrhea in patients with acquired immune deficiency syndrome (AIDS) are underway. Because the currently available treatments for cryptosporidiosis in AIDS often result in unsuccessful outcomes, there will be interest in off-label use of this drug in VA patients; therefore, the 2 published articles using NTZ in cryptosporidiosis in AIDS are reviewed.[3, 4]

CLINICAL DATA
Giardia lamblia)
The discussion will be limited to trials conducted in adults. Study RM01-3011was a randomized, placebo-controlled trial conducted in Peru and Egypt in non-immunodeficient patients ≥ 12 years old (see appendix for details).[1] The primary objective was to demonstrate superiority in clinical response of nitazoxanide tablets compared to placebo. The secondary objectives included demonstration of non-inferiority of nitazoxanide tablets compared nitazoxanide suspension and parasitological response. Patients were randomized to receive nitazoxanide tablets 500mg twice daily, nitazoxanide suspension 500mg twice daily, or placebo for 3 days. Concentrated and unconcentrated stool samples were microscopically examined for detection of cysts of *G. lamblia* using either immunofluorescence assay or enzyme immunoassay. Patients were evaluated for clinical response and parasitological response at days 7-10. Additionally, a single stool sample from those patients who were clinically well at day 7-10 was tested for cysts of *G. lamblia* between days 14-17. A clinical assessment was not performed at this time.

The following definitions were used:

Clinical improvement at day 7 (± 2 days)
Well- no sx's, no watery stools, < 2 soft stools and no hematochezia w/i past 24h, or no sx's and no unformed stools w/i past 48h
Continuing illness- any number of watery stools, > 2 soft stools per 24h, or hematochezia or enteric sx's plus the passage of any number of soft or watery stools during the past 48h

Parasitological response (2 stool samples collected at least 24h apart between days 7-10)
Eradication- no oocysts in either posttreatment stool sample
Persistence- oocysts in one or both posttreatment stool samples

Patients in the NTZ tablet group showed significantly greater clinical improvement than the placebo group (85% vs. 44%). NTZ tablets were found to be non-inferior to NTZ suspension. There was a weak correlation between parasitological response and clinical response. For example, in the NTZ tablet group, clinical response was 85% while parasitological response was 56%. There was a difference in parasitological response when results were broken down by country. In Peru, where *G. lamblia* is hyperendemic, a higher percentage of patients were positive for cysts. The investigators attributed this to either continuous ingestion of *Giardia* cysts during treatment and followup or in cases of heavy colonization, some cysts may remain sequestered in the small bowel after treatment.

Sixteen patients, who had eradicated cysts at day 7-10 and were clinically well, were again positive for cysts at days 14-17 (7 NTZ-tab, 6 NTZ-susp, and 3 placebo).

Cryptosporidiosis in immunocompetent patients (not approved by the FDA)
Rossignol et al. conducted a randomized, placebo controlled trial in immunocompetent adults/adolescents and children (see appendix for details).[2] The discussion will be limited to adult/adolescent subgroup. Patients were randomized to NTZ 500mg BID for 3 days or placebo. Definitions as described in the

Giardia study were used. The primary endpoints were clinical and parasitological outcomes. Clinical improvement occurred in 72% and 44% of patients in the NTZ and placebo groups respectively (p=0.0845) and parasitological improvement in 60% and 24% respectively (p=0.0219).

Cryptosporidiosis and HIV(not approved by the FDA)

The published data for use in HIV-positive patients are very limited. In a double-blind study conducted in Zambia, 50 HIV-negative and 50 HIV-positive children with diarrhea due to *Cryptosporidium parvum* were randomized to receive NTZ 100mg BID x 3 days or placebo.[3] The mean CD4 count in the HIV-positive children was 620 cells/mm^3. Children were hospitalized for the duration of the study and received supportive therapy that included hydration, antibiotics, micronutrients, and nutritional support. The primary endpoint was clinical response on day 7 after the start of treatment and was defined as no symptoms, no watery stools, and $\leq$ 2 soft stools/24 hours OR no symptoms and no unformed stools within the past 48 hours. The secondary endpoint was parasitological response, which was defined as no oocysts in stool sample on post-treatment days 7 and 8. Treatment with NTZ led to a clinical and parasitological response in the HIV-negative children; however, in the HIV-positive children, the drug was no more effective than placebo.

Table 1. Response rates during double-blind phase

	HIV-negative		HIV-positive	
	Nitazoxanide	**Placebo**	**Nitazoxanide**	**Placebo**
Clinical response	56%	23%	8%	25%
Parasitological response	52%	14%	16%	21%
Mortality rate	0%	18%	20%	17%

After a 5-day follow-up period, those children not responding were offered an additional 3-day course of treatment on an open-label basis. Twenty-four HIV-positive (13 originally assigned to NTZ and 11 originally assigned to placebo) and 19 HIV-negative children (12 originally assigned to NTZ and 7 originally assigned to placebo) received open-label treatment. Improved response rates were seen in both groups.

Table 2. Response rates during open-label treatment

	HIV-negative		HIV-positive	
	Originally on Nitazoxanide	**Originally on Placebo**	**Originally on Nitazoxanide**	**Originally on Placebo**
Clinical response	92%	86%	77%	55%
Parasitological response	50%	43%	35%	33%

In a double-blind study conducted in Mexico, 66 HIV-positive patients aged 18-65 years were randomized to receive nitazoxanide 500mg BID, nitazoxanide 1gm BID, or placebo for 14 days.[4] Patients had to be positive for *C. parvum* oocyst in stool and have diarrhea for more than 2 weeks with more than 4 liquid or semisolid evacuations daily. Parasitological cure was defined as 3 consecutive negative fecal examinations for *C. parvum.* Clinical cure was defined as complete resolution of diarrhea and other symptoms of cryptosporidiosis on days 15 and 29 for the active treatment groups and on day 15 for the placebo group.

The mean CD4 count was 98.97 ± 94.56 with 85% of patients receiving antiretroviral therapy (mostly zidovudine) and 6 % receiving protease inhibitors. When looking at completer data, 63-67% of those in the nitazoxanide groups achieved parasitological cure compared to 25% on placebo. Individuals who had a parasitological cure were more likely to have a clinical cure. In a subgroup of 15 patients who had CD4 counts $\leq$ $50mm^3$, the parasitological response did not differ from that of placebo.

Table 3. Response rates in adult trial

	500mg BID	**1000mg BID**	**Placebo**
Parasitological cure (Completers / ITT)	63%* / 46%	67%^ / 43.5%	25% / 23.8%
Clinical cure (completers)	63%	60%	50%
Clinical cure in those who had parasitological cure	92%	80%	-
Clinical cure in those who did not have parasitological cure	14%	20%	-

ITT= intent-to-treat; *p=0.016; ^p=0.013

METABOLISM
NTZ is rapidly hydrolyzed to an active metabolite, desacetyl-nitazoxanide and is then conjugated primarily via glucuronidation. NTZ is highly protein bound, therefore caution should be used when co-administering with other highly protein bound drugs. Nitazoxanide has a very weak affinity for CYP3A (IC_{50} 152μM) and shows no appreciable inhibition of CYP2D6 (IC_{50} 755μM). (Data from Romark laboratories)

SAFETY AND TOLERANCE
Nitazoxanide was well tolerated. In the controlled and uncontrolled clinical trials in patients ≥ 12y/o (n=1628), the most commonly reported adverse events that were seen more frequently with NTZ than placebo were headache, diarrhea, and nausea.[1]

DOSE
The dose for the treatment of diarrhea caused by *Giardia lamblia* in patients ≥ 12 years old is 500mg every 12 hours for 3 days. It is recommended that the dose be taken with food.

COST
Nitazoxanide is available as a 500mg tablet and as a suspension 100mg/5cc. The cost of the 500mg tablet is $7.21/tablet and the 60cc bottle of the suspension is $34.55. Nitazoxanide suspension is packaged as an unsuspended powder and requires reconstitution with 48mL of water. Once reconstituted, the suspension can be stored at room temperature for 7 days.

Table 4. Cost of treatment of Giardia lamblia

Treatment of *Giardia lamblia*	FSS cost per unit	Cost of treatment
Nitazoxanide • 500mg tablets every 12 hours x 3 days • 25 cc (500mg) every 12 hours x 3 days	$7.21	$43.26 $103.65
Metronidazole 250mg TID x 5 days	$0.02-0.08	0.30-1.20
Tinidazole 2g as a single dose	$2.65/250mg tablet	$21.20
Paromomycin 25-35mg/kg/day divided into 3 doses x 7 days	$0.99/250mg capsule	Price will vary based on dose used and patient weight

***C. parvum* in HIV-positive adults (off-label use)**
If one were to use the low-dose of 500mg BID x 14 days as described in Rossignol et al, the cost of therapy would be $202 (using tablets). A 14-day course of generic paromomycin 500mg TID is $83.16, although longer courses may be necessary.

REFERENCES
1. FDA website http://www.fda.gov/cder/foi/nda/2004/21-497_21-498s001_Alinia.htm

2. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by Cryptosporidium parvum: a prospective randomized, double-blind, placebo-controlled study of nitazoxanide. J Infectious Dis 2001; 184:103-106.

3. Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis; a randomized controlled trial. Lancet 2002; 360: 1375-80

4. Rossignol JF, Hidalgo H, Feregrino M, et al. A double-'blind' placebo-controlled study of nitazoxanide in the treatment of cryptosporidial diarrhoea in AIDS patients in Mexico. Trans R Soc Trop Med Hyg 1998; 92: 663-66.

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Appendix: Clinical trials in immunocompetent adults/adolescents

<table>
<tr><th>STUDY</th><th>INCLUSION</th><th>DOSAGE</th><th>BASELINE DATA</th><th>RESULTS</th></tr>
<tr>
<td>RM01-3011
R, DB, PC
N=135

Study conducted in Peru and Egypt</td>
<td>≥ 12y/o
Immunocompetent
> 3 bowel movements/day AND > 1 of the following: abdominal pain, nausea, vomiting, tenesmus, malabsorption

G. lamblia cysts in stool sample within 7 days of enrollment</td>
<td>2:2:1 randomization

NTZ 500mg tablet BID x 3 days

NTZ suspension 25cc (500mg) BID x 3 days

Placebo BID x 3 days

Doses taken with food</td>
<td>Age (years): NTZ-tab 20 ± 10.3; NTZ-susp 20 ± 10.2; PL 19 ± 7.1

3-4 stools/day (% pts.): NTZ-tab 94%; NTZ-susp 92%; PL 63%

5-10 stools/day (% pts.): NTZ-tab 4%; NTZ-susp 6%; PL 0

Liquid stools (% pts.): NTZ-tab 22%; NTZ-susp 16%; PL 9%

Duration of diarrhea (days): NTZ-tab 5.74 ± 2.5; NTZ-susp 6.41 ± 3.52; PL 6.59 ± 2.95

Giardia cysts (concentrated stool)- NTZ-tab 6.2 ± 11.7; NTZ-susp 5.3 ± 9; PL 6.5 ± 8.1

Mean ± SD</td>
<td>
<table>
<tr><th></th><th>NTZ tablets n/N (%)</th><th>NTZ susp n/N (%)</th><th>Placebo n/N (%)</th></tr>
<tr><td>Clinical response (day 7-10)</td><td></td><td></td><td></td></tr>
<tr><td>• All patients</td><td>46/54 (85%)</td><td>45/54 (83%)</td><td>12/27 (44%)</td></tr>
<tr><td>• Peru only</td><td>29/36 (81%)</td><td>29/36 (81%)</td><td>9/18 (50%)</td></tr>
<tr><td>• Egypt only</td><td>17/18 (94%)</td><td>16/18 (89%)</td><td>3/9 (33%)</td></tr>
<tr><td>Parasitological response-eradication (day 7-10)</td><td></td><td></td><td></td></tr>
<tr><td>• All patients</td><td>30/54 (56%)</td><td>26/54 (48%)</td><td>5/27 (19%)</td></tr>
<tr><td>• Peru only</td><td>13/36 (36%)</td><td>11/36 (31%)</td><td>3/18 (17%)</td></tr>
<tr><td>• Egypt only</td><td>17/18 (94%)</td><td>15/18 (83%)</td><td>2/9 (22%)</td></tr>
<tr><td>Clinical responder with parasitological persistence (day 7-10)</td><td></td><td></td><td></td></tr>
<tr><td>• All patients</td><td>18/46 (39%)</td><td>19/45 (42%)</td><td>8/12 (67%)</td></tr>
<tr><td>• Peru</td><td>17/29 (59%)</td><td>18/29 (62%)</td><td>6/9 (67%)</td></tr>
<tr><td>• Egypt</td><td>1/17 (6%)</td><td>1/16 (6.3%)</td><td>2/3 (67%)</td></tr>
<tr><td>Parasitological response (day 14-17)*</td><td></td><td></td><td></td></tr>
<tr><td>• All patients</td><td>22/45 (49%)</td><td>24/43 (56%)</td><td>3/12 (25%)</td></tr>
<tr><td>• Peru</td><td>6/29 (21%)</td><td>10/27 (37%)</td><td></td></tr>
<tr><td>• Egypt</td><td>16/16 (100%)</td><td>14/16 (88%)</td><td></td></tr>
</table>
*Parasitological response was evaluated in the patients who were clinical responders at day 7-10
Significant difference for tablet vs. placebo
NTZ tablets non-inferior to suspension
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<tr>
<td>Rossignol
R, DB, PC
N=50
Study conducted in Egypt

50 children were also enrolled. Results for adults/adolescents only are presented</td>
<td>12-65y/o
Immunocompetent
Diarrhea (> 4 unformed stools/d)
C. parvum oocysts in stool sample
No use of antiprotozoal drug within 2 weeks of enrollment</td>
<td>NTZ 500mg tablet BID x 3 days vs. placebo

Doses taken with food</td>
<td>5-10 stools per/day n=49
> 10 stools per/day n=1
Liquid stools n=11

<u>Mean duration of diarrhea*</u>
NTZ: 13.22 days (median 9 days)
Placebo: 12.76 days (median 9.5 days)

*values for adults and children combined; values for adults only not given</td>
<td>
<table>
<tr><th></th><th>NTZ</th><th>Placebo</th><th>p-value</th></tr>
<tr><td>Clinical improvement</td><td>18/25 (72%)</td><td>11/25 (44%)</td><td>0.0845</td></tr>
<tr><td>Eradication</td><td>15/25 (60%)</td><td>6/25 (24%)</td><td>0.0209</td></tr>
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