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. Because this drug only has a pediatric indication at this time, a full review was not conducted. Safety and efficacy has not been established in HIV positive patients or patients with immunodeficiency. Phase III clinical trials using a tablet formulation for the treatment diarrhea caused by *Cryptosporidium parvum* and *Giardia lamblia*, in non-immunodeficient adolescents and adults, and 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. (Amadi et al. Lancet 2002; 360: 1375-80; Rossingnol et al. Trans R Soc Trop Med Hyg 1998; 92: 663-66)

CLINICAL DATA IN CRYPTOSPORIDIOSIS AND HIV
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. 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 NTZ and 11 originally assigned 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. 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. The most common adverse event reported was vomiting and was considered as possibly related to therapy. There were also 4 cases of anemia – 1 new onset and 3 with progression of baseline abnormalities consistent with AIDS.

COST

Nitazoxanide is available as a suspension 100mg/5cc 60ml bottle at a cost of $35.93. If one were to use the low-dose of 500mg BID x 14 days as described in Rossignol et al, it would require the use of 12 bottles at a total cost of $431. A 14-day course of generic paromomycin 500mg TID is $83.16, although longer courses may be necessary.

The tablets are available through a compassionate access program by enrolling in the "Compassionate Use Study of NTZ for the Treatment of Cryptosporidiosis in AIDS Patients." For information on obtaining nitazoxanide tablets through the compassionate access program please contact Romark at compassionateaccess@romark.com.

RECOMMENDATION

It is recommended that nitazoxanide not be added to the national or VISN formulary at this time and to revisit this topic when data for use in HIV positive adults becomes available. Clinicians are encouraged to contact the sponsor to see if their patient qualifies for the compassionate access program.

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