Nitazoxanide

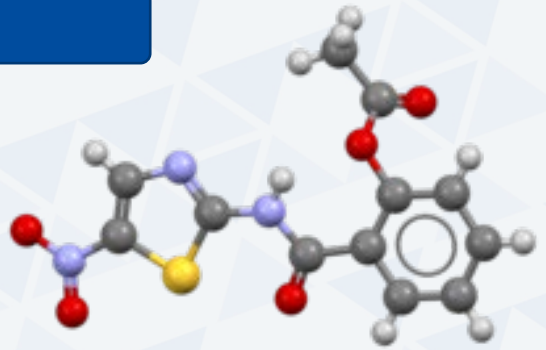
A Review of Pertinent Drug Information for SARS-CoV-2

Nina Maguire, PharmD
Clinical Pharmacy Specialist, Infectious Diseases
Penn Presbyterian Medical Center
Christina.Maguire@pennmedicine.upenn.edu
@stenotrophonina

Data as of May 17, 2021

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide



1975: developed as veterinary antihelminthic

1984: efficacy noted against human tapeworms

1990s: antiviral activity first noted

2002: FDA Approved

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Rossignol JF, et al. Am J Trop Med Hyg. 1984;33(3):511-12. https://doi: 10.4269/ajtmh.1984.33.511
Stachulski AV, et al. J Med Chem. 2011;54(12):4119-32. https://doi.org/10.1021/jm200153p

Indications

- FDA approved indications
  - Diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*
- Outside of United States
  - Used commonly as broad spectrum antiparasitic agent
  - Latin America, Egypt, India, and Bangladesh approved widely for treatment of infections caused by intestinal protozoa and helminths
  - Approved in Brazil for treatment of norovirus and rotavirus

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide [package insert]. Tampa, FL 33607: Romark, L.C.; 2016
Rossignol JF. J Infect Public Health. 2016;9(3):227-30. https://doi.10.1016/j.jiph.2016.04.001
Stachulski AV, et al. ACSA Infect Dis. 2020. https://doi: 10.1021/acsinfecdis.0c00478

Spectrum of Activity

Antiprotozoal

- *Entamoeba histolytica*
- *Cystoisospora belli*
- *Blastocystis hominis*
- *Giardia lamblia*
- *Cryptosporidium parvum*

Antihelminthic

- *Taenia saginata*
- *Hymenolepis nana*
- *Fasciola hepatica*
- *Strongyloides stercoralis*

Anti(myco)bacterial

- *Clostridoides difficile*
- *Mycobacterium tuberculosis*
- *Helicobacter pylori*

Antiviral

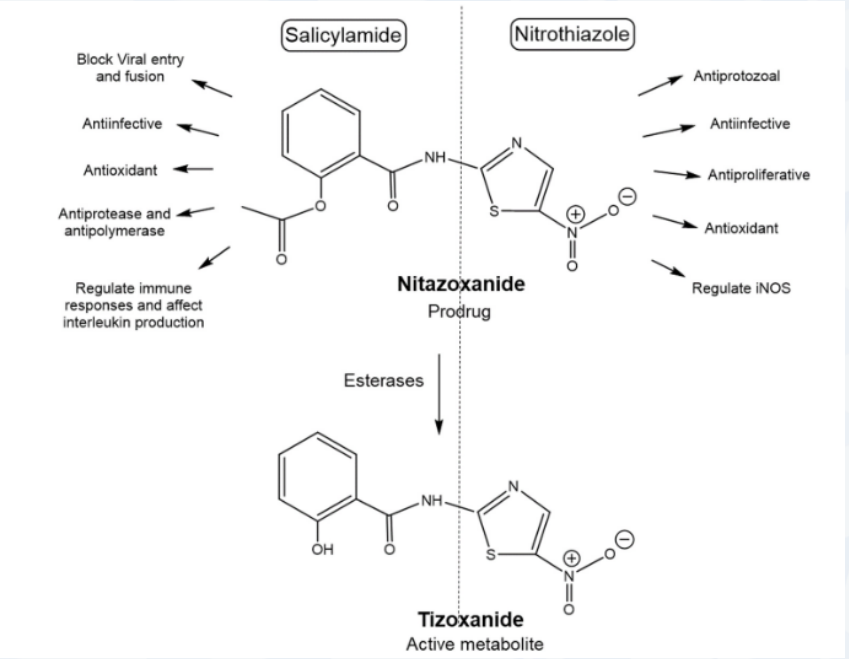
- Influenza A and B
- RSV
- Parainfluenza
- Coronavirus
- Rotavirus
- Norovirus
- Hepatitis B and C

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide [package insert]. Tampa, FL 33607: Romark, L.C.; 2016
Rossignol JF. J Infect Public Health. 2016;9(3):227-30. https://doi.10.1016/j.jiph.2016.04.001
Rossignol JF. Antiviral Res. 2014;110:94-103. https://doi.10.1016/j.antiviral.2014.07.014
Korba BE, et al. Antiviral Res. 2008;77(1):56-63. https://doi.10.1016/j.antiviral.2007.08.005
Megraud F, et al. Antimicrob Agents Chemother. 1998;42(11);2836-40. https://doi.10.1128/AAC.42.11.2836

Mechanism of Action

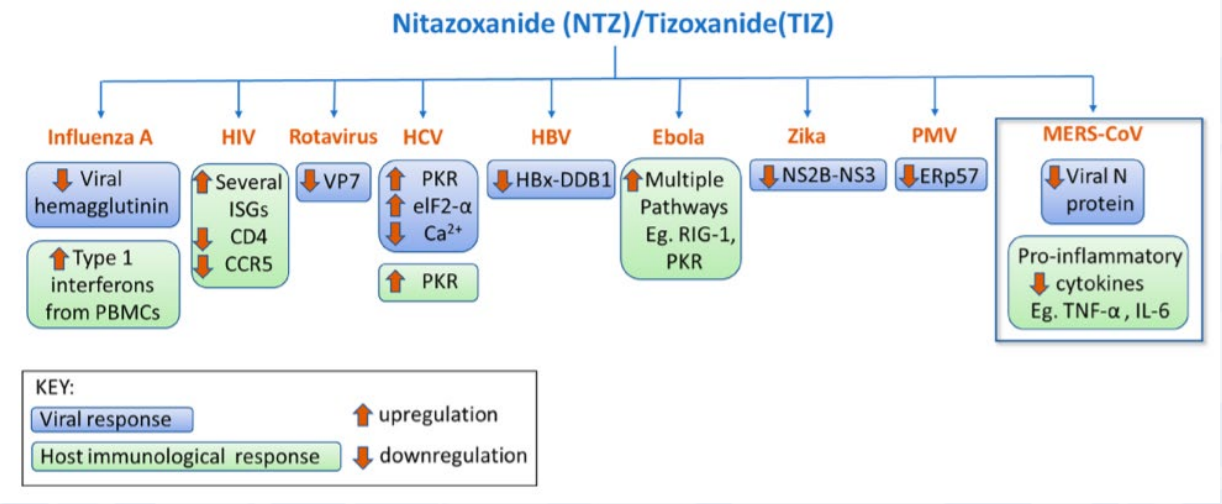
Inhibits pyruvate-ferredoxin oxidoreductase (PFOR), which is an enzyme essential for metabolism in **anaerobic bacteria and parasites**



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hemphill A, et al. Expert Opin Pharmacother. 2006;7:953-64. https://doi: 10.1517/14656566.7.953
Lokhande AS, et al. Eur J Pharmacol. 2021;891:173748. https://doi:10.1016/j.ejphar.2020.173748

Mechanism of Action



- Possible role in endosomal and non-endosomal of COVID-19 cell fusion and entry

- Inhibits TNF-α, IL-2, IL-4, IL-5, IL-6, IL-8, and IL-10
- 90% *in vivo* reduction of IL-6 after one time dose in mice

- Modulates UPR signaling to promote antioxidant response
- Inhibits DPI to prevent cell damage

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stachulski AV, et al. ACSA Infect Dis. 2020. https://doi: 10.1021/acsinfecdis.0c00478
Hong SK, et al. Int Immunopharmacol. 2012;13:23-7. https://doi:10.1016/j.intimp.2012.03.002

Dosing

- Available as 500 mg tablets and oral suspension (100 mg/5 mL)

Age	Dosage	Duration
1 - 3 years	100 mg/5 mL oral suspension every 12 hours	3 days
4 - 11 years	200 mg/10 mL oral suspension every 12 hours	
12 years and older	500 mg tablet every 12 hours	

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide [package insert]. Tampa, FL 33607: Romark, L.C.; 2016.

Pharmacokinetics

Absorption

- Suspension bioavailability compared to tablet is 70%
- C_{max}: 5.49 – 10.6 µg/mL
- T_{max}: 3.0 – 5.49 hours

Distribution

- 99.9% protein bound

Metabolism

- Hydrolyzed hepatically to active metabolite, tizoxanide

Elimination

- $T_{1/2}$: 1.3 hours
- Excreted primarily in feces (66%) and urine (33%)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide [package insert]. Tampa, FL 33607: Romark, L.C.; 2016.
Broekhuysen J, et al. 2000;38(8):387-94. https://doi.org/10.5414/cpp33387

Adverse Reactions

- Most common adverse reactions include
  - Abdominal pain
  - Headache
  - Chromaturia
  - Nausea
- Post marketing surveillance reports
  - Diarrhea, dizziness, dyspnea, rash, urticaria

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide [package insert]. Tampa, FL 33607: Romark, L.C.; 2015.

Drug-Drug Interactions

- Not metabolized by CYP450 system
- Some caution with use of other highly protein bound agents with narrow therapeutic index (i.e. warfarin)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide [package insert]. Tampa, FL 33607: Romark, L.C.; 2015.

Clinical Pearls

- Tablets ≠ suspension
- Take tablets or suspension with food
  - AUC is increased 2x and C_{max} increased by 50% in tablets
  - AUC is increased 45-50% and C_{max} increased by $\leq$ 10% in oral suspension
- Extended release product (300 mg) being used in ongoing clinical trials

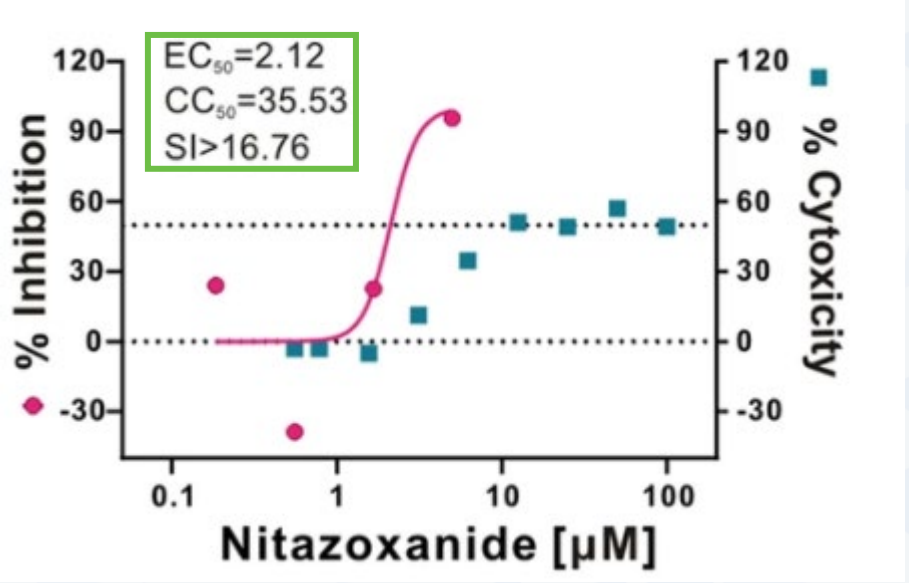
SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide [package insert]. Tampa, FL 33607: Romark, L.C.; 2016.

In Vitro Data

- Measured cytotoxicity, virus yield, and infection rates of nine different compounds
- Outperformed by remdesivir and chloroquine in regards to selectivity index

Vero E6 Cells Infected with 2019-nCoV at 48 hours



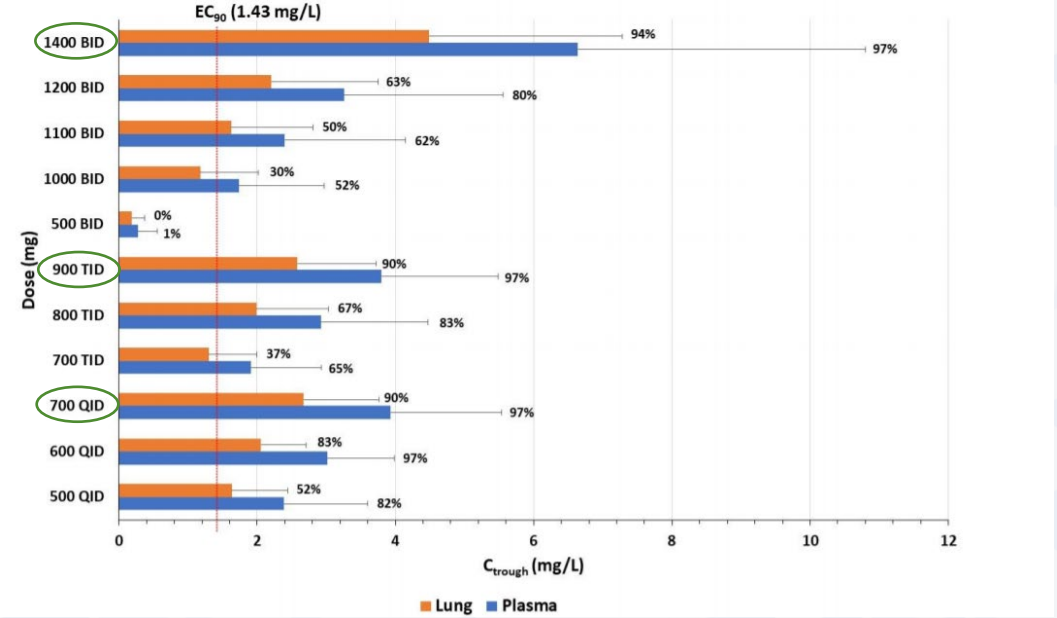
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Wang M, et al. Cell Res. 2020;30(3):269-71. https://doi.org/10.1038/s41422-020-0282-0

Dosing Strategies

Based on physiologically based pharmacokinetic analysis and assumed gastrointestinal tolerance, **700 mg q6hr or 900 mg q8hr** dosing is needed to achieve EC_{90} for SARS-CoV-2.

Predicted Tizoxanide C_{trough} with Various Dosing Strategies



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

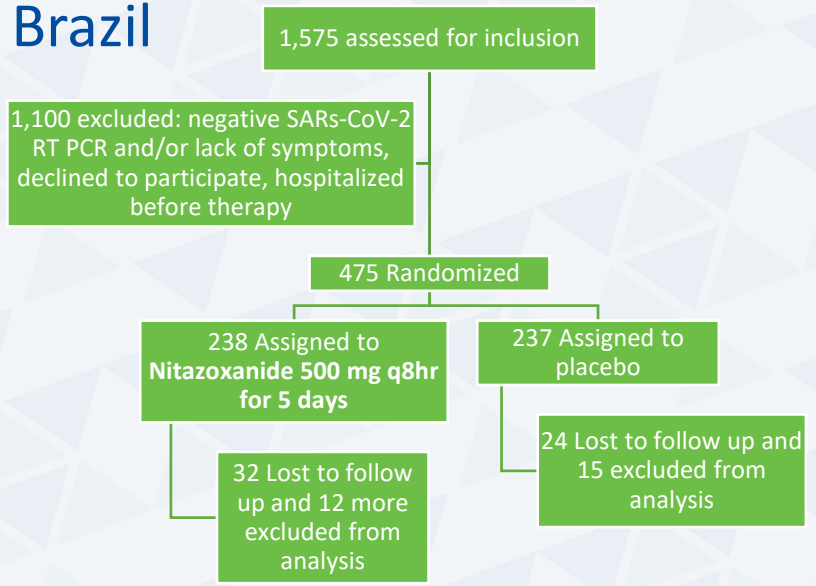
Rajoli RKR, et al. Br J Clin Pharmacol. 2021;87(4):2078-88. https://doi.org/10.1111/bcp.14619

SARITA-2 Trial

- Double blind, placebo controlled trial
- 5 urgent care centers and 2 hospitals in Brazil

	Nitazoxanide (n = 194)	Placebo (n = 198)
Age 18 to 39 years, n (%)	115 (59)	113 (57)
Male sex, n (%)	101 (52)	83 (42)
Ethnicity, n (%)		
White	131 (68)	138 (70)
Black	31 (16)	32 (16)
Asian	5 (3)	2 (1)
Presence of comorbidities*, n (%)	23 (12)	36 (18)
3 days of symptoms prior to enrollment, n (%)	138 (71)	125 (63)

*Comorbidities: hypertension, diabetes, asthma

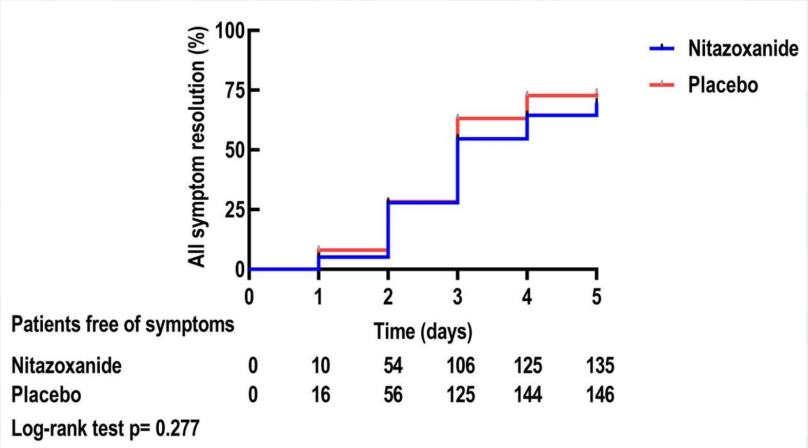


SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

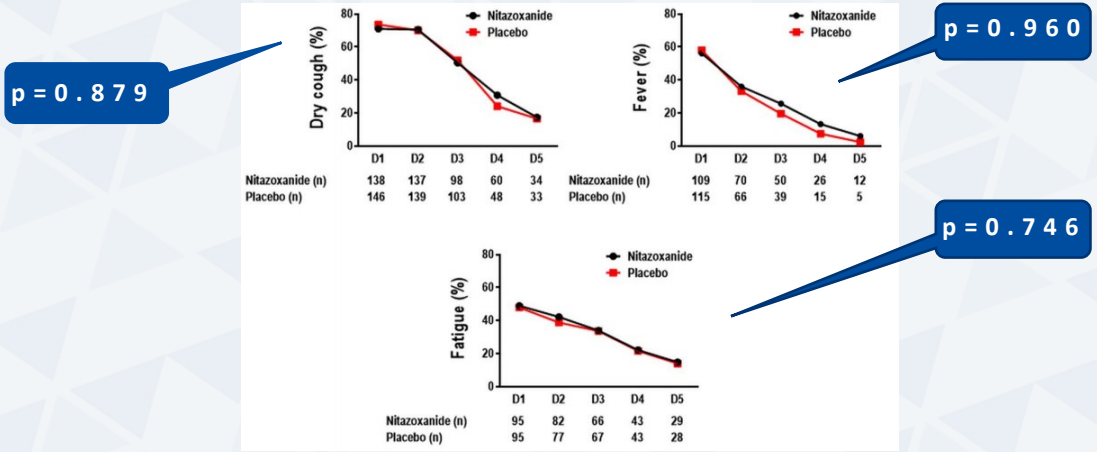
Rocco PRM, et al. Eur Resp J. 2020;ahead of print. https://doi:10.1183/13993003.03725-2020

SARITA-2 Trial

Primary outcome: resolution of symptoms at day 5 of therapy



Breakdown of Composite Outcome by Symptom



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Rocco PRM, et al. Eur Resp J. 2020;ahead of print. https://doi:10.1183/13993003.03725-2020

SARITA-2 Trial

	Nitazoxanide (n = 194)	Placebo (n = 198)	p value
PCR Viral Load (log10 copies/mL), median (IQR)	3.63 (0 – 5.03)	4.13 (2.88 – 5.31)	0.006
PCR Positive, n (%)	136 (70)	162 (82.2)	0.009
WBC (x10^3), median (IQR)	6.1 (5.1 – 7.3)	6.4 (5.3 – 7.8)	0.080
Platelets (x10^3/mL), median (IQR)	240 (209 – 288)	239 (198 – 285)	0.078
CRP (mg/L), median (IQR)	5.0 (1.0 – 16.2)	4.5 (2.0 – 13.0)	0.275

Conclusions:

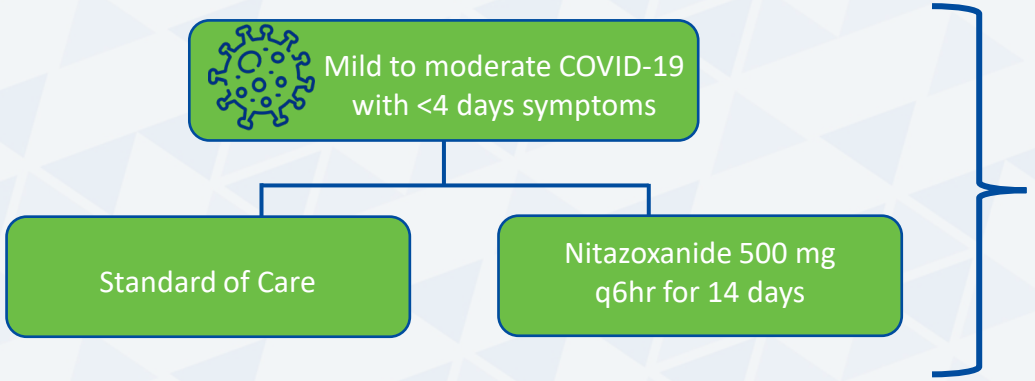
Nitazoxanide **did not affect symptom resolution after 5 days** of therapy in ambulatory patients but **did reduce viral load significantly** with no serious adverse events.

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Rocco PRM, et al. Eur Resp J. 2020;ahead of print. https://doi:10.1183/13993003.03725-2020

Nitazoxanide Viral Load Reduction

- Randomized, placebo-controlled, single blinded pilot study
- **Primary endpoint**: viral eradication on day 7 of treatment



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Silva M, et al. medRxiv. 2021;ahead of print. https://doi.org/10.1101/2021.03.03.21252909

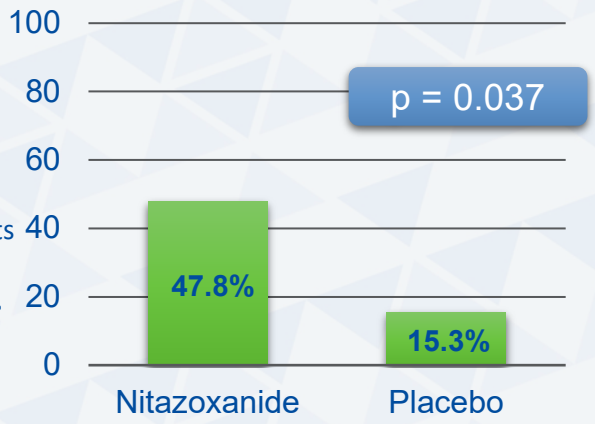
Nitazoxanide Viral Load Reduction

	Nitazoxanide (n = 23)	Placebo (n = 13)
Age, median (range)	44 (19 – 67)	53 (28 – 68)
Male sex, n (%)	17 (73.9)	9 (63.9)
Hospitalized with mild disease without oxygen therapy, n (%)	16 (72)	9 (75)
Oxygen Saturation, median percentage (range)	97 (94 – 100)	96 (93 – 98)

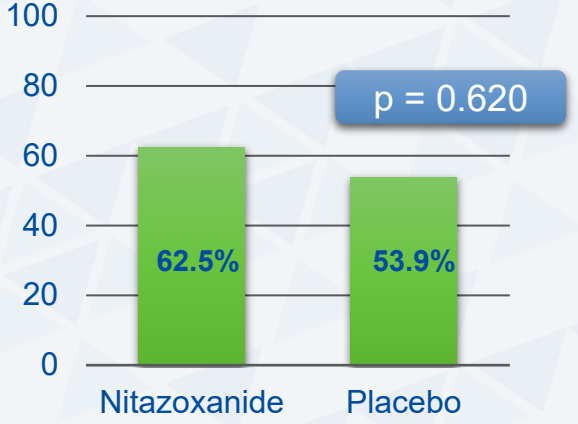
Conclusions:

Nitazoxanide outperformed placebo in the number of patients with **viral loads reduced by at least 35%** in mild to moderate COVID-19, but **did not affect rates of undetectable viral loads.** Further clinical outcomes are needed.

Percent Achieving a Viral Load Reduction ≥ 35%



Percent with Undetectable Viral Load at Day 7



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Silva M, et al. medRxiv. 2021;ahead of print. https://doi.org/10.1101/2021.03.03.21252909

Current Clinical Trials

23 trials pending

Completed with Results Pending

- Nitazoxanide + sofosbuvir/ledipasvir
- Monotherapy (moderate to severe)
- Monotherapy (prophylaxis)
- Nitazoxanide + azithromycin + dutasteride
- Nitazoxanide 600 mg q12hr x 5 days

Active/Recruiting

- Monotherapy (6)
- Pre/post exposure prophylaxis (4)
- Nitazoxanide + ivermectin
- Nitazoxanide + hydroxychloroquine + ivermectin
- Nitazoxanide + atazanavir
- Nitazoxanide + ribavirin + ivermectin
- Nitazoxanide + ribavirin + hydroxychloroquine
- Nitazoxanide + ribavirin
- Nitazoxanide + hydroxychloroquine
- Nitazoxanide + investigational drug
- Nitazoxanide + favipravir

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

ROMARK ANNOUNCES INITIAL RESULTS OF PHASE 3 CLINICAL TRIAL OF NT-300 TABLETS FOR THE TREATMENT OF COVID-19

– NT-300 reduced progression to severe COVID-19 disease by 85%

– Romark is working with FDA and plans to seek Emergency Use Authorization in the U.S.

www.clinicaltrials.gov Accessed 05/17/2021
www.romark.com Accessed 05/17/2021

Take Home Points

- Nitazoxanide is a relatively expensive (in the United States) agent with both antiviral and anti-inflammatory properties
- Current COVID-19 guidelines do not mention use of nitazoxanide
- Nitazoxanide appears to lower viral load in mild COVID-19, which is of unclear clinical significance
- Additional clinical data is needed to evaluate nitazoxanide's role in treatment of COVID-19

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Nitazoxanide

A Review of Pertinent Drug Information for SARS-CoV-2

Nina Maguire, PharmD
Clinical Pharmacy Specialist, Infectious Diseases
Penn Presbyterian Medical Center
Christina.Maguire@pennmedicine.upenn.edu
@stenotrophonina

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Data as of May 17, 2021