SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PROTOZOX TABLET (Nitazoxanide Tablets 500mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Nitazoxanide

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitazoxanide Tablets 500mg is an antiprotozoal indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*.

4.2 Posology and method of Administration

Important Administration Instructions for Pediatric Patients 11 years of Age or Younger:
Nitazoxanide tablets should not be administered to pediatric patients 11 years of age or younger because a single tablet contains a greater amount of Nitazoxanide than the recommended dosing in this pediatric age group.

Recommended Dosage

Age	Dosage
12 years and older	Nitazoxanide Tablets 500mg every 12 hours with food

4.3 Contraindications

Hypersensitivity
Nitazoxanide Tablets is contraindicated in patients with a prior hypersensitivity to Nitazoxanide or any other ingredient in the formulations.

4.4 Special warnings and special precautions for use

Not available

4.5 Interaction with other medicinal products and other forms of interaction

Highly Protein Bound Drugs with Narrow Therapeutic Indices
Tizoxanide (the active metabolite of Nitazoxanide) is highly bound to plasma protein (>99.9%). Therefore, monitor for adverse reactions 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

There are no data with Nitazoxanide tablets in pregnant women to inform a drug-associated risk. No teratogenicity or fetotoxicity was observed in animal reproduction studies with administration of Nitazoxanide to pregnant rats and rabbits during organogenesis at exposure 30 and 2 times, respectively, the exposure at the maximum recommended human dose of 500 mg twice daily based on body surface area (BSA).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Nitazoxanide was administered orally to pregnant rats at doses of 0, 200, 800 or 3200 mg/kg/day on gestation days 6 to 15. Nitazoxanide produced no evidence of systemic maternal toxicity when administer once daily via oral gavage to pregnant female rats at levels up to 3200 mg/kg/day during the period of organogenesis.

In rabbits, Nitazoxanide was administered at doses of 0, 25, 50, or 100 mg/kg/day on gestation days 7 to 20. Oral treatment of pregnant rabbits with nitazoxanide during organogenesis resulted in minimal maternal toxicity and no external fetal anomalies.

Lactation

Risk Summary

No information regarding the presence of Nitazoxanide in human milk, the effects on the breastfed infant, or the effects on milk production is available. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Nitazoxanide tablets and any potential adverse effects on the breastfed infant from Nitazoxanide tablets or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of Nitazoxanide Tablets for the treatment of diarrhea caused by *G. lamblia* or *C. parvum* in pediatric patients 12 to 17 years of age has been established based on three (3) randomized controlled studies with 47 pediatric subjects treated with Nitazoxanide Tablets 500 mg.

A single Nitazoxanide Tablets contains a greater amount of Nitazoxanide than is recommended for use in pediatric patients 11 years or younger. [see Dosage and Administration]

Geriatric Use

Clinical studies of Nitazoxanide Tablets 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 Nitazoxanide Tablets.

Renal and Hepatic Impairment
The pharmacokinetics of Nitazoxanide in patients with compromised renal or hepatic function has not been studied.

HIV-Infected or Immunodeficient Patients
Nitazoxanide Tablets have not been studied for the treatment of diarrhea caused by G. lamblia in HIV-infected or immunodeficient patients. Nitazoxanide Tablets have not been shown to be superior to placebo for the treatment of diarrhea caused by C. parvum in HIV-infected or immune deficient patients [see Clinical Studies]

4.7 Effects on ability to drive and use machines

Not available

4.8 Undesirable effects

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Nitazoxanide Tablets was evaluated in 2177 HIV-uninfected subjects 12 months of age and older who received Nitazoxanide Tablets at the recommended dose for at least three days in pooled controlled clinical trials involving 536 HIV-uninfected subjects treated with Nitazoxanide Tablets, the most common adverse reactions were abdominal pain, headache, chromaturia and nausea (≥2%).

Safety data were analyzed separately for 280 HIV-uninfected subjects ≥12 years of age receiving Nitazoxanide Tablets at the recommended dose for at least three days in 5 placebo-controlled clinical trials and for 256 HIV-uninfected subjects 1 through 11 years of age in 7 controlled clinical trials. there were no differences between the adverse reactions reported for Nitazoxanide Tablets - treated subjects based upon age.

Postmarketing Experience
The following adverse reactions have been identified during post approval use of Nitazoxanide Tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. the following is a list of adverse reactions spontaneously reported with Nitazoxanide Tablets which were not included in clinical trial listings:
Gastrointestinal disorders: diarrhea, gastroesophageal reflux disease
Nervous system disorders: dizziness
Espiratory, thoracic and mediastinal disorders: dyspnea
Skin and subcutaneous tissue disorders: rash, urticarial

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org' Overdose

Limited information on Nitazoxanide over dosage is available. In the event of overdose, gastric lavage may be appropriate soon after oral administration. Patients should be observed and given symptomatic and supportive treatment. There is no specific antidote for overdose with Nitazoxanide Tablets 500mg. Because tizoxanide is highly protein bound (>99.9%), dialysis is unlikely to significantly reduce plasma concentrations of the drug.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotosoal

ATC code: P01AX11

Mechanism of Action

Mechanism of Action - Nitazoxanide is an antiprotozoal - Pharmacokinetics - Absorption - Single Dosing: Following oral administration.

5.2 Pharmacokinetic properties

Absorption
Single Dosing:
Following oral administration of Nitazoxanide Tablets, the parent drug, Nitazoxanide, is not detected in plasma. The pharmacokinetic parameners of the metabolites, tizoxanide and tizoxanide glucuronide are shown in Tables 2 and 3 below.

Table 2. Mean (+/- SD) plasma pharmacokinetic parameters of tizoxanide and tizoxanide glucuronide following administration of a single dose of one 500 mg Nitazoxanide Tablets with food to subjects ≥12 years of age

Tizoxanide				**Tizoxanide Glucuronide**		
Age	C_{max} ((µg/mL)	T_{max} (hr)	AUC_t µg• hr/m	C_{max} ((µg/mL)	T_{max} (hr)	AUC_t 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)

Multiple dosing:
Following oral administration of a single Nitazoxanide Tablets every 12 hours for 7 consecutive days, there was no significant accumulation of nitazoxanide metabolites tizoxanide or tizoxanide glucuronide detected in plasma.

Bioavailability:

Nitazoxanide Tablets were administered with food in clinical trials and hence they are recomended to be administered with food [see Dosage and Administration]

Distribution
In plasma, more than 99% of tizoxanide is bound to proteins

Elimination
Metabolism
Following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation.

Excretion
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.

Specific Populations
Pediatric Patients
The pharmacokinetics of tizoxanide and tizoxanide glucuronide following administration of Nitazoxanide Tablets in pediatric patients 12-17 years of age are provided above in Table 2. The pharmacokinetics of tizoxanide and tizoxanide glucuronide following administration of Nitazoxanide Tablets in pediatric patients 1-11 years of age are provided above in Table 3.

Drug Interaction Studies
In vitro studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes.

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 G. lamblia directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The DNA-derived PFOR protein sequence of C. parvum appears to be similar to that of G. lamblia. Interference with the PFOR enzyme-dependent electron transfer reaction may not be the only pathway by which nitazoxanide exhibits antiprotozoal activity.

Resistance
A potential for development of resistance by C. parvum or G. lamblia to nitazoxanide has not been examined.

Antimicrobial Activity
Nitazoxanide and its metabolite, tizoxanide, are active in vitro in inhibiting the growth of (i) sporozoites and oocysts of C. parvum and (ii) trophozoites of G. lamblia.

Susceptibility Test Methods
For protozoa such as C. parvum and G. lamblia, standardized tests for use in clinical microbiology laboratories are not available.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies have not been conducted.

Mutagenesis

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 (TA100) in the Ames bacterial mutation assay.

Impairment of Fertility

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).

CLINICAL STUDIES

Diarrhea Caused by *G. lamblia*

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

In a double-blind, controlled trial (Study 1) conducted in Peru and Egypt in adults and adolescents with diarrhea and with one or more enteric symptoms (e.g., abdominal pain, nausea, vomiting, fever, abdominal distention, loss of appetite, flatulence) caused by *G. lamblia*, a three-day course of treatment with Nitazoxanide Tablets 500mg administered 500 mg twice daily was compared with a placebo tablet for 3 days. A second double-blind, controlled trial (Study 2) conducted in Egypt in adults and adolescents with diarrhea and with or without enteric symptoms (e.g., abdominal colic, abdominal tenderness, abdominal cramps, abdominal distention, fever, bloody stool) caused by *G. lamblia* compared Nitazoxanide Tablets administered 500 mg twice daily for 3 days to a placebo tablet. 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:

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

	Nitazoxanide Tablets 500mg	**Placebo Tablets**
Study 1	85% (46/54) ¶ §	44% (12/27)

Study 2	100% (8/8)	30% (3/10)

*Includes all patients randomized with *G. 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 is (-14%, 17%).
Some patients with 'well' clinical responses had *G. 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 *C. parvum*

Diarrhea caused by *C. parvum* in adults and adolescents 12 years of age or older:

In a double-blind, controlled trial conducted in Egypt in adults and adolescents with diarrhea and with or without enteric symptoms (e.g., abdominal pain/cramps, nausea, vomiting) caused by *C. parvum*, a three-day course of treatment with Nitazoxanide Tablets administered 500 mg twice daily was compared with a placebo tablet for 3 days. 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 within the past 24 hours' or 'no symptoms and no unformed stools within the past 48 hours.' The following clinical response rates were obtained:

Table 6. Clinical Response Rates in Adult and Adolescent Patients 4 to 7 Days Post-therapy% (Number of Successes/Total)

	Nitazoxanide 500mg Tablets	**Placebo Tablets**
Intent-totreat analysis*	96% (27/28) ¶ §	41% (11/27)

*Includes all patients randomized with *C. parvum* as the sole pathogen. Patients failing to complete the study 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.
In a second double-blind, placebo-controlled study of nitazoxanide tablets conducted in Egypt in adults and adolescents with diarrhea and with or without enteric symptoms (e.g., abdominal colic, abdominal cramps, epigastric pain) caused by *C. parvum* as the sole pathogen, clinical and parasitological response rates showed a similar trend to the first study. Clinical response rates, evaluated 2 to 6 days following the end of treatment, were 71% (15/21) in the nitazoxanide group and 42.9% (9/21) in the placebo group.
Some patients with 'well' clinical responses had *C. parvum* oocysts 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 *C. parvum* in pediatric patients 1 through 11 years of age:

In two double-blind, controlled trials in pediatric patients with diarrhea and with or without enteric symptoms (e.g., abdominal distention, colic, left iliac fossa tenderness) caused by *C. parvum*, a three-day course of treatment with nitazoxanide (100 mg twice daily in pediatric

patients ages 12-47 months, 200 mg twice daily 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 within the past 24 hours' or 'no symptoms and no unformed stools within the past 48 hours.' The following clinical response rates were obtained:

Table 7. Clinical Response Rates in Pediatric Patients 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 patients with 'well' clinical responses had *C. parvum* 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.

Diarrhea caused by *C. parvum* in Acquired Immune Deficiency Syndrome (AIDS) patients :

A double-blind, placebo-controlled trial did not produce clinical cure rates that were significantly different from the placebo control when conducted in hospitalized, severely malnourished pediatric patients with acquired immune deficiency syndrome (AIDS) in Zambia.

5.3 Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

Corn starch (Extra white maize), Pregelatinized starch, Sodium Starch Glycolate, Type A, Hypromellose (Methocel E15 Premium LV), Purified water, Sodium Starch Glycolate, Talc, Magnesium Stearate. Opadry AMB.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Stored below 30º C

6.5 Nature and contents of pack's

1x10 Alu-Alu Blister packs

6.6 Instructions for use, handling and disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorization Holder:
Sai Pharmaceuticals,

Whitefield Edge,

Nairobi, Kenya.

8. Marketing Authorization Number

H2022/CTD6405/2150ER

9. Date of first Authorization /renewal of the authorization
2022 January 11

10. Date of revision of the Text
2022 January 11