1.4.1

Summary of Product Characteristics) Protozox

1. NAME OF THE MEDICINAL PRODUCT

PROTOZOX Powder for suspension
Nitazoxanide 100 mg/ 5 mL Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION1

Each 1.53 gm of powder to make 5 ml protozox oral suspension contains 100 mg nitazoxanide.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Protozox for Oral Suspension (100 mg/5 mL)

Light red to rose homogenous powder formulation that, when reconstituted as directed, contains 100 mg nitazoxanide/5mL. The reconstituted suspension has a pink color and strawberry flavor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum:*

Protozox for Oral Suspension (patients 1 year of age and older) is indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*.

Limitations of Use Protozox for Oral Suspension have not been shown to be effective for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients.

4.2 Posology and method of administration

Posology

Table 1. Recommended Dosage

Age	Dosage	Duration
1-3 years	5 mL of Protozox for Oral Suspension (100 mg nitazoxanide) taken orally every 12 hours with food	3 days
4-11 years	10 mL of Protozox for Oral Suspension (200 mg nitazoxanide) taken orally every 12 hours with food	
12 years and older	25 mL of Protozox for Oral Suspension (500 mg nitazoxanide) taken orally every 12 hours with food	

Directions for Mixing Protozox for Oral Suspension

Reconstitute Protozox for Oral Suspension as follows:

- Measure 48 mL of water for preparation of the 100 mg/5 mL suspension.
- Tap the bottle until all powder flows freely.
- Add approximately one-half of the 48 mL of water required for reconstitution and shake vigorously to suspend the powder.
- Add the remainder of water and shake vigorously again.

Keep the container tightly closed, and shake the suspension well before each administration. The reconstituted suspension may be stored for 7 days at room temperature, after which any unused portion must be discarded.

4.3 CONTRAINDICATIONS

Protozox for Oral Suspension are contraindicated in patients with a prior hypersensitivity to nitazoxanide or any other ingredient in the formulations.

4.4 Special warnings and precautions for use

Geriatric Use

Clinical studies of nitazoxanide for Oral Suspension 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.

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 for Oral Suspension have not been studied for the treatment of diarrhea caused by *G. lamblia* in HIV-infected or immunodeficient patients. Nitazoxanide for Oral Suspension have not been shown to be superior to placebo for the treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients.

Pediatric Population

The safety and efficacy of nitazoxanide for Oral Suspension for the treatment of diarrhea caused by *G. lamblia* or *C. parvum* in pediatric patients 1 to 11 years of age has been established based on three (3) randomized, controlled studies with 104 pediatric subjects treated with nitazoxanide for Oral Suspension 100 mg/5 mL. Furthermore, the safety and efficacy of nitazoxanide for Oral Suspension 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 two (2) randomized controlled studies with 44

pediatric subjects treated with nitazoxanide for Oral Suspension 100 mg/5 mL.

Safety and efficacy of nitazoxanide for Oral Suspension in pediatric patients less than one year of age has not been studied.

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 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 exposures 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 administered 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.

Breastfeeding

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 and any potential adverse effects on the breastfed infant from nitazoxanide or from the underlying maternal condition.

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).

4.7 Effects on the ability to drive and use machines

No available data.

4.8 Undesirable effects

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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 was evaluated in 2177 HIV-uninfected subjects 12 months of age and older who received nitazoxanide for Oral Suspension at the recommended dose for at least three days. In pooled controlled clinical trials involving 536 HIV-uninfected subjects treated with nitazoxanide for Oral Suspension, 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 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-treated subjects based upon age.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of nitazoxanide. 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 which were not included in clinical trial listings: *Gastrointestinal disorders*: diarrhea, gastroesophageal reflux disease *Nervous System disorders:* dizziness *Respiratory, thoracic and mediastinal disorders*: dyspnea *Skin and subcutaneous tissue disorders:* rash, urticaria

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'

4.9 Overdose

Limited information on nitazoxanide overdosage 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. Because tizoxanide is highly protein-bound (>99.9%), dialysis is unlikely to significantly reduce plasma concentrations of the drug.

5. Pharmacological properties

5.1 Pharmacodynamics properties

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.

5.2 Pharmacokinetics

Absorption

Single Dosing:

Following oral administration of Protozox Oral Suspension, the parent drug, nitazoxanide, is not detected in plasma. The pharmacokinetic parameters of the metabolites, tizoxanide and tizoxanide glucuronide are shown in Table 2 below.

Table 2. Mean (±SD) plasma pharmacokinetic of tizoxanide and tizoxanide glucuronide parameter values following administration of a single dose of nitazoxanide for Oral Suspension with food to subjects ≥1 year of age

		Tizoxanide			**Tizoxanide Glucuronide**		
Age	Dose	C_{max} (µg/mL)	*T_{max} (hr)	AUCinf (µg•hr/mL)	C_{max} (µg/mL)	*T_{max} (hr)	AUC_{inf} (µg•hr/mL)
1-3	100	3.11	3.5 (2-	11.7 (4.46)	3.64 (1.16)	4.0 (3-4)	19.0 (5.03)

years	mg	(2.0)	4)				
4-11 years	200 mg	3.00 (0.99)	2.0 (1-4)	13.5 (3.3)	2.84 (0.97)	4.0 (2-4)	16.9 (5.00)
≥18 years	500 mg	5.49 (2.06)	2.5 (1-5)	30.2 (12.3)	3.21 (1.05)	4.0 (2.5-6)	22.8 (6.49)

* T_{max} is given as a Mean (Range)

Bioavailability:

When nitazoxanide for Oral Suspension was administered with food, the AUCt of tizoxanide and tizoxanide glucuronide increased by about 45-50% and the C_{max} increased by ≤10%.

Nitazoxanide for Oral Suspension were administered with food in clinical trials and hence they are recommended to be administered with food.

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 (desacetylnitazoxanide). 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 for Oral Suspension in pediatric patients 1-11 years of age are provided above in Table 2. Mean (±SD) plasma pharmacokinetic of tizoxanide and tizoxanide glucuronide parameter values following administration of a single dose of nitazoxanide for Oral suspension with food to subjects ≥1 year of age.

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

6. Pharmaceutical particulars

6.1 List of excipients

Avicel

Xanthan gum

Sodium benzoate

Aerosil 200

Erythrosine Lake

Citric acid anhydrous

Maize starch

Sucrose extra fine

Strawberry flavor.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

See outer pack.

6.4 Special precautions for storage

-Store at a temperature not exceeding 30°C. After reconstitution, keep for one week at a temperature not exceeding 30°C.

-The reconstituted suspension may be stored for 7 days at room temperature, after which any unused portion must be discarded

- Keep out of reach of children

- Carton box contains an amber (type III) glass bottle containing 16.2 gm powder to make 60 ml suspension, polyethylene terephthalate (PET) closure with foamed high-density polyethylene lining, a measuring (LDPE) plastic cup, and insert leaflet.

7 Marketing authorization holder

Sai Pharmaceuticals,

Whitefield Edge,

Nairobi, Kenya.

8. Marketing authorization number(s)

H2022/CTD6406/2151ER

9. Date of first authorization/renewal of the authorization

2022 January 11

10. Date of revision of the text

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