SUMMARY OF PRODUCT CHARACTERISTICS
(ZINRO)

1. **Name of the medicinal product**
Ornidazole 0.5% w/v Solution for Infusion.

2. Qualitative and quantitative composition
Each 100 ml of solution for infusion contains 0.5 g Ornidazole.
Excipients: Each 100 ml of solution for infusion contains 0.9 g Sodium Chloride.

For full list of excipients, see section 6.1

3. Pharmaceutical form
Solution for infusion

Description: It is a clear almost colourless to pale yellow sterile solution packed in LDPE bottles.

4. Clinical particulars
4.1 Therapeutic indications
• Anerobic systemic infections caused by Ornidazole –sensitive microflora: septicemia, meningitis,
peritonitis, post-operative wound infections, post-natal sepsis, septic abortion and endometritis;

• Prevention of infections caused by anaerobic bacteria, during operative treatment (especially middle and straight intestine surgeries) gynaecological surgeries;

• Severe intestinal ameobiasis, all extra-intestinal amoebiasis forms, giardiasis, liver abscess. 4.2 Posology and method of administration Ornidazole is given by mouth in tablets after food, or intravenously. When given intravenously, solutions of Ornidazole should be diluted to 5 mg or less per mL and 100 or 200 mL infused over 15 to 30 minutes.

It has also been given by vaginal pessary. In amebiasis, 500 mg of ornidazole is given twice daily by mouth for 5 to 10 days. Patients with amebic dysentery may be given 1.5 g as a single daily dose for 3 days. In severe amebic dysentery and amebic liver abscess, ornidazole may be given by intravenous infusion in a dose of 0.5 to 1 g initially, followed by 500 mg every 12 hours for 3 to 6 days. In giardiasis, 1 or 1.5 g of drug is given by mouth as a single daily dose for 1 or 2 days.

In trichomoniasis, a single dose of 1.5 g is given by mouth or 1 g by mouth together with 500 mg vaginally is given; alternatively, a 5-day course of ornidazole 500 mg twice daily by mouth, with or without 500 mg vaginally, is also used. Sexual partners should be treated concomitantly. For the treatment of anaerobic bacterial infections, ornidazole is given by intravenous infusion in an initial dose of 0.5 to 1 g, followed by 500 mg every 12 hours for 5 to 10 days; oral therapy with 500 mg every 12 hours should be substituted as soon as possible.

For the prevention of post-operative anaerobic bacterial infections, 1 g is given by intravenous infusion about 30 minutes before surgery. Ornidazole is an effective and safe drug for the treatment of active Crohn's disease. It has also been used as maintenance treatment with promising results.

4.2 Posology and Method of Administration
Ornidazole is given to patients in doses of 20 mg/kg BW (body weight) per day in two separate doses for the treatment. Mechanism of action could be related either to its action against anaerobes or on the immune system. Ornidazole is one of the most frequently used antibiotics

for curing Helicobacter pylori infection. In the treatment, 500 mg Ornidazole is used with 30 mg lansoprazole and 1 g Amoxicillin.

4.3 Contraindications
• Hypersensitivity to any of the drug components
• Organic central nervous system diseases;
• Epilepsy, disseminated sclerosis;
• Circulation disorders;
• Chronic alcoholism;
• First pregnancy trimester and lactation;
• Body mass under 6 kg.

4.4 Special warnings and precautions for use
Caution should be exercised in patients with diseases of the CNS, e.g., epilepsy or multiple sclerosis. A health risk exists, among others, in patients with liver disease, in alcoholics, epileptics, in patients with brain damage, in pregnant and nursing women, and children, if the special dosage for children is exceeded. The effect of other medicines can be intensified or impaired. Nitro-imidazoles are generally considered mutagenic chemicals.

The nitrogen group present in nitroimidazole derivatives is considered responsible for the mutagenicity of these compounds. In a study, mutagenicity was observed with Klebsiella pneumoniae and Salmonella typhimurium Ornidazole was revealed to be mutagenic in Salmonella typhimurium, but negative results have been observed in other tests, such as micro nucleus in mice and chromosome aberrations. Long-term carcinogenicity studies were also conducted with ornidazole (high dose 400 mg/kg/day) by administering in rats for two years. At the end of this study no carcinogenicity was recorded for ornidazole.

4.5 Interaction with other medicinal products and other forms of interaction
Ornidazole potentiates the effect of the coumarine range oral anticoagulants, which requires appropriate adjustment of the dose of the latter. Ornidazole prolongs the myo-relaxing effect of vecuronium bromide. The drug's concentration is lowered in case of concurrent administration of microsomal enzyme inducers (phenobarbital, rifampicin) and increases in case of concurrent administration of liver microsomal system inhibitors, particularly H2-receptor blockers (cimetidine). Isolated cases of peripheral nephritis, psychic depression and epilepsy-like convulsions were reported in cases of concurrent use of other 5-nitroimidazole derivatives. Alcoholism: Ornidazole, the therapeutic use of which is quite distinct from the treatment of chronic alcoholism, may produce a disulfram-like reaction with alcohol (flushing of the face and neck, palpitations, dizziness, nausea, etc.) in some cases.

The mechanism of this reaction is thought to be related with an inhibition of acetaldehyde dehydrogenase. Patients should be warned against the possibility of interactions with alcohol.

4.6 Fertility, Pregnancy and lactation
Like other nitro-imidazoles, ornidazole is widely distributed in the body, cross the placenta and appears in breast milk.

When administered during pregnancy: No teratogenic effect was observed with ornidazole in mice, rats and rabbits. Local and systemic tolerability of ornidazole was excellent in humans when used in pregnancy, and patients showed complete remission without premature delivery. Children born to the trial patients showed normal initial development and their growth was normal. There was no evidence of ornidazole accumulation, and the pharmacokinetic parameters were very similar to those seen in healthy subjects. Therefore, dosage regimen requires no adjustment during pregnancy.
Fertility: Ornidazole has the advantage of fewer side effects in rats in which species its anti-fertility action has been documented, it has contraceptive properties in male, but not female,

rats. It produces infertility by inhibiting epididymal sperm motility in terms of decreased sperm velocity. These effects are rapidly reversible after the cessation of treatment.

4.7 Effects on ability to drive and use machines
Effects on ability to drive and use machines Somnolence, dizziness, tremor, rigidity, poor coordination, seizures, vertigo, or temporary loss of consciousness may occur in patients receiving ZINRO. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive

4.8 Undesirable effects
Serious and Otherwise Important Adverse Reactions The following serious and otherwise important adverse reactions are as follows Tendinopathy and Tendon Rupture.
• QT Prolongation
• Hypersensitivity Reactions
• Other Serious and Sometimes Fatal Reactions
• Central Nervous System Effects
• Clostridium difficile-Associated Diarrhoea
• Peripheral Neuropathy
• Photosensitivity/Phototoxicity
• Development of Drug Resistant Bacteria

4.9 Overdose
No specific counter measures after accidental overdose are recommended. In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Symptoms: loss of consciousness, headache, vertigo, trembling, convulsions, depression, peripheral nephritis, nausea, vomiting. Treatment: symptomatic treatment, specific antidote unknown.

5. Pharmacological Properties
5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Antibacterials for systemic use; Imidazole derivatives,
ATC code: J01X D03 5-Nitroimidazoles belong to the nitroheterocyclic family of compounds widely used for the treatment or prophylaxis of infections due to anaerobic bacteria and protozoa. They have also received much attention in cancer therapy as radio sensitizers of hypoxic tumors and by their direct cytotoxic effects towards hypoxic cells. Nitroimidazoles are thought to produce their bactericidal activity through four phases:

(I) Entry into the bacterial cell
(II) Nitro group reduction
(III) Action of the cytotoxic by products
(IV) Production of inactive end products

Bactericidal activity appears to be dependent on the formation of a redox intermediate metabolite in the bacterium. This toxic metabolite may interact primarily with DNA, RNA or intracellular proteins; however, its main effects are DNA strand breakage, inhibited repair and ultimately disrupted transcription and cell death. Owing to its similar chemical properties, Ornidazole shares the same mechanism of action and spectrum of microbiological activity as other nitro imidazole agents against anaerobes and protozoa. Therefore, it is a drug of choice for treatment of a large variety of diseases, including intra-abdominal, pulmonary and brain abscesses, chronic sinusitis and otitis, and genital tract infections.

5.2 Pharmacokinetic properties
Absorption: The absolute bio-availability of Ornidazole is >90 percent administered dose.

Dose (mg)	n	Schedule F(%)	C_{max} (mg/mL)	V_{ss} (L/kg)	AUC24h (mg/L.h)	$t_{1/2\beta}$ (h)	Cl (L/h)[a]
1500 PO	50	S	23.6 (1h)			10.9	
1000 IV	14	S	24	0.9[b]		14.1	2.82
750 PO	4	S	10.9	0.87		14.4	
1500 PO	5	S	31.5			13.8	
1000 IV	10	S		0.86		14.1	3.04
20 mg/kg IV	12 (neonates/infants)	S		0.96	511	14.7	0.80 mL/min/kg
1000 IV or PO	8 (with variable renal function)	S 102(n=6)		0.70	311 (PO)	12.7	2.94
500 IV	8 (CRF, no dialysis)	S		0.73	185.0[c]	10.8	2.78
500 IV	7 (dialysis)	S					3.84
1000 IV or PO	6 (dialysis)	S 97 (n=2)		0.78	308	11.0	3.91
500 IV	5 (CAPD)	S		0.79	185.6[c]	11.8	2.87
	10 (cirrhosis)	S		0.84		21.9	2.09
	10 (cirrhosis)	S		0.81		19.3	2.24
	10 (hepatitis)	S		0.90		19.3	2.01
	10 (CA)	S		0.74		17.4	1.57
	11 (liver transplant)	S		9.11			
1000 IV	5 (PG)	M	20.71	0.79	375c	15.2	3.4

[a] Normalized to a bodyweight of 70 kg. [b] Approximate value [c] AUC from zero to infinity

AUC24 = area under the concentration-time curve over 24 hours; **CA**=pancreatic cancer; **CAPD**=continuous ambulatory peritoneal dialysis; **Cl**=total body clearance; C_{max}=peak plasma drug concentration; **CRF**=cronic renal failure; **F**=bioavailability; **IV**=intravenous; **M**=multiple; **n**=number of participants; **PG**=pregnant; **PO**=oral; **S**=single; $t_{1/2\beta}$=elimination half-life; V_{ss}=volume of distribution at steady state.

Distribution: Ornidazole is widely distributed in body tissues and fluids, including cerebro spinal fluid. Antibacterial concentrations are achieved in vaginal secretions, appendix and intestinal tissues. Ornidazole concentrations have been measured in the colonic (8.7µg/g) and abdominal (3.6 to 4.4 µg/g) walls and epiploic fat (3.4 to 4.7µg/g) throughout colorectal surgery in those receiving a 1 g intravenous dose for surgical prophylaxis. Although ornidazole concentrations in cerebro spinal fluid have only been assessed in animal models, it is expected that it should penetrate the central nervous system.

Metabolism: Ornidazole is extensively metabolized in the liver before excretion by renal pathway. Ornidazole is largely excreted in the urine and to a lesser extent in the faeces, mainly as conjugates and metabolites. Only 4% of unchanged drug was excreted in the urine.

Excretion: The plasma elimination half-life of ornidazole is 11 to 14 hours with AUC values for single intravenous 500 mg doses of 185 mg/L.h and for 1 g doses of 375 mg/L.h. The mean Cl value of ornidazole is 47 mL/min (2.82 L/h) for 1 g intravenous dose.

5.3 Preclinical safety data

The acute oral LD50 of ornidazole in rats is 1.780 mg/kg. Reported LD50 value for mice is 1.420 mg/kg orally. Ornidazole administrated orally in mice at a dose level of 400 mg/kg/day for 13 weeks did not produce any toxicity except weight loss. Nitro-imidazoles are generally considered mutagenic chemicals.

The nitrogen group present in nitroimidazole derivatives is considered responsible for the mutagenicity of these compounds. In a study, mutagenicity was observed with Klebsiella pneumoniae and Salmonella typhimurium. Ornidazole was revealed to be mutagenic in Salmonella typhimurium, but negative results have been observed in other tests, such as micro nucleus in mice and chromosome aberrations. Long-term carcinogenicity studies were also conducted with ornidazole (high) dose 400 mg/kg/day) by administering in rats for two years. At the end of this study no carcinogenicity was recorded for ornidazole.

Like other nitroimidazoles, ornidazole is widely distributed in the body, cross the placenta and appears in breast milk. When administered during pregnancy, no teratogenic effect was observed with ornidazole in mice, rats and rabbits. Ornidazole has the advantage of fewer side

effects in rats in which species its antifertility action has been documented. It has contraceptive properties in male, but not female, rats. It produces infertility by inhibiting epididymal sperm motility in terms of decreased sperm velocity. These effects are rapidly reversible after the cessation of treatment.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium chloride B.P, Hydrochloric acid B.P, Sodium hydroxide B.P and Water for Injections B.P.

6.2 Incompatibilities

Vecuronium
Warfarin

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C, but do not freeze.

6.5 Nature and contents of container Pack sizes:

100 mL
The Low Density Polyethylene plastic are overwrapped with a protective BOPP film and final packed in mono carton a long with product leaflet.

6.6 Special precautions for disposal and other handling

Ornidazole containers are for single use only.
Discard any unused portion.
Do not reconnect partially used containers.
LDPE plastics containers are recyclable.

7. Marketing authorisation holder

Abacus Parenteral Drugs Limited, Uganda Block 191, Plot no.114, Kinga Mukono,
P.O. Box 31376, Kampala, Uganda.

8. Marketing Authorisation Number(s):

TAN 22 HM 0105

9. Date of first Authorisation/renewal of the Authorisation:

11/04/2022

10. Date of revision of the text