MODULE 1.3 SOUTH AFRICAN LABELLING AND PACKAGING

1.3.1 South African Package Insert
1.3.1.1 Package Insert

PROPOSED PACKAGE INSERT – CLEAN COPY

1	**SCHEDULING STATUS:** **S3**
2 3 4	**PROPRIETARY NAME** (and dosage form)**:** **FRUSEMIDE DEZZO 10 mg/ml** (Injection)
5 6 7	**COMPOSITION:** Contains 10,00 mg frusemide per ml. The excipients are: sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.
8 9	**PHARMACOLOGICAL CLASSIFICATION:** A 18.1 Diuretics
10 11 12 13 14	**PHARMACOLOGICAL ACTION:** **Pharmacodynamic properties:** Frusemide is a loop diuretic which inhibits the reabsorption of sodium and water. It is an inhibitor of the Na+-K+-2Cl- symporter in the thick ascending limb of the loop of Henle. The thick ascending limb has a great reabsorptive capacity and reabsorbs most of the rejectate

15	from the proximal tubule. Therefore, inhibitors of the Na+-K+-2Cl- symport are often called
16	high-ceiling diuretics. The action of frusemide in the thick ascending limb of the loop of Henle
17	is due to a combination of two factors: (1) Approximately 25 % of the filtered Na+ load
18	normally is reabsorbed by the thick ascending limb, and (2) nephron segments past the thick
19	ascending limb do not possess the reabsorptive capacity to rescue the flood of rejectate
20	exiting the thick ascending limb.
21	**Pharmacokinetic properties:**
22	The half-life of frusemide is up to about 2 hours although it is prolonged in neonates and in patients with
23	renal and hepatic impairment. After intravenous injection its effects are evident in about 5 minutes and last
24	for about 2 hours. Frusemide is up to 99 % bound to plasma albumin. Frusemide metabolism occurs
25	predominantly in the kidney, and is mainly excreted in the urine, largely unchanged. Clearance reduces
26	with increasing age, renal impairment and cardiac disease. There is also some excretion via the bile and
27	non-renal elimination is considerably increased in renal impairment. Frusemide crosses the placental
28	barrier and is distributed into breastmilk. The clearance of frusemide is not increased by haemodialysis
29	**INDICATIONS:**
30	Fluid retention associated with ascites due to cirrhosis of the liver or congestive cardiac
31	failure.
32	Renal oedema (fluid retention) associated with nephrotic syndrome (if diuretic treatment is
33	required).
34	As an adjunct in acute pulmonary oedema.
35	Support measures in cerebral oedema.

36	Hypertension or a hypertensive crisis (as supportive measure).
37	Forced diuresis.
38	**CONTRAINDICATIONS:**
39	FRUSEMIDE DEZZO 10 mg/ml is contraindicated in patients with hypersensitivity to
40	frusemide or to any of the other ingredients of FRUSEMIDE DEZZO 10 mg/ml or to other
41	sulphur containing medicines such as sulfonamides.
42	Patients with anuria or those with renal failure caused by nephrotoxic or hepatotoxic
43	medicines, or in renal failure associated with hepatic coma.
44	Patients with uraemia and oliguria during treatment of severe progressive renal disease.
45	FRUSEMIDE DEZZO 10 mg/ml should not be given in pre-comatose or comatose states
46	associated with hepatic encephalopathy.
47	Breast-feeding women.
48	Patients with hypovolaemia or dehydration.
49	Patients with severe hypokalaemia or hyponatraemia.
50	**WARNINGS AND SPECIAL PRECAUTIONS:**
51	Tinnitus and deafness may occur, in particular during rapid, high dose administration.

Deafness may be permanent, especially in patients taking other ototoxic medicines (see INTERACTIONS). To reduce the risk of ototoxicity, FRUSEMIDE DEZZO 10 mg/ml should not be injected intravenously at a rate exceeding 4 mg/minute.

- FRUSEMIDE DEZZO 10 mg/ml is considered unsafe in porphyric patients as frusemide has been associated with acute attacks of porphyria.
- Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

Particular careful monitoring is necessary in:

- Patients with hypotension, who are at risk from a pronounced fall in blood pressure.
- Patients with diabetes or latent diabetes.
- Patients with gout.
- Patients with hepatorenal syndrome.
- Patients with hypoproteinaemia. Cautious dose titration is required.
- Premature infants (renal function must be monitored).
- Patients liable to electrolyte deficiency – monitoring of electrolytes is required (see CONTRAINDICATIONS).
- Patients at risk for radiocontrast nephropathy. FRUSEMIDE DEZZO 10 mg/ml is not recommended.

Urinary output must be secured. FRUSEMIDE DEZZO 10 mg/ml should be used with care in patients with partial obstruction or urinary outflow such as patients with prostatic hyperplasia or impairment of micturition since it can precipitate acute urinary retention.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

The ability to drive or operate machinery may be impaired, especially at the commencement

75 76	of treatment or when changing over from other medicines or when alcohol is consumed during FRUSEMIDE DEZZO 10 mg/ml therapy.
77 78 79 80 81 82 83 84 85 86 86.1 87 88 89 90 91	**INTERACTIONS:** **Lithium salts:** FRUSEMIDE DEZZO 10 mg/ml may cause an increase in the plasma lithium concentration when given concurrently. **Hypnotics (chloral hydrate):** A syndrome of flushing, tachycardia, elevated blood pressure and severe diaphoresis has been reported following administration of FRUSEMIDE DEZZO 10 mg/ml with chloral hydrate. **Probenecid:** When probenecid is administered concurrently, it may reduce the renal clearance of FRUSEMIDE DEZZO 10 mg/ml and cause a reduction in the diuretic effect. **Methotrexate:** FRUSEMIDE DEZZO 10 mg/ml and methotrexate may both affect the renal elimination of each other. This could result in a reduced effect of FRUSEMIDE DEZZO 10 mg/ml, or conversely with a resultant increase in plasma levels of methotrexate. **Blood pressure increasing sympathomimetics:** Hypokalaemia may be enhanced by concomitant administration. FRUSEMIDE DEZZO 10 mg/ml may also diminish the response to pressor amines, such as noradrenaline. **Theophylline:** Concomitant administration may result in decreased theophylline concentrations.

Antiepileptics: The diuretic effect of FRUSEMIDE DEZZO 10 mg/ml may be reduced when phenytoin is administered simultaneously.

Phenobarbital plasma concentrations may be increased by simultaneous administration of FRUSEMIDE DEZZO 10 mg/ml.

Concurrent administration of carbamazepine may result in hyponatraemia.

Risperidone: An increased mortality has been reported in elderly patients with dementia who were administered risperidone and FRUSEMIDE DEZZO 10 mg/ml simultaneously.

Antidiabetics: FRUSEMIDE DEZZO 10 mg/ml may antagonize the effect of hypoglycaemic medicines in diabetic patients.

Digoxin treatment: When digoxin is administered concurrently, it should be remembered that potassium deficiency increases the sensitivity of the myocardium to digoxin.

Ototoxic medicines: FRUSEMIDE DEZZO 10 mg/ml can enhance the ototoxicity of aminoglycoside antibacterials (eg. kanamycin, gentamycin, tobramycin) and other ototoxic medicines (such as cisplatin). The hearing defects that result may be irreversible (see WARNINGS AND SPECIAL PRECAUTIONS). FRUSEMIDE DEZZO 10 mg/ml should be given in low doses with a positive fluid balance when used to achieve forced diuresis during cisplatin treatment to prevent ototoxicity and nephrotoxicity.

Nephrotoxic medicines: The nephrotoxic effects of cephalosporin antibiotics such as cefalotin may be enhanced by FRUSEMIDE DEZZO 10 mg/ml.

Corticosteroids: May cause sodium retention, and increase the risk of hypokalaemia.

Hypotensive medicines: The action of other hypotensive medicines may be potentiated by FRUSEMIDE DEZZO 10 mg/ml. Especially in combination with ACE-inhibitors a marked fall in blood pressure and deterioration in renal function including renal failure may be seen.

Diuretics: Severe electrolyte disturbances may occur in patients given metolazone with FRUSEMIDE DEZZO 10 mg/ml. Some electrolyte disturbances (eg. hypokalaemia, hypomagnesaemia) may increase the toxicity of other medicines inducing QT interval prolongation syndrome.

NSAIDs including acetylsalicylic acid: NSAIDs may antagonise the diuretic effect of FRUSEMIDE DEZZO 10 mg/ml. Use of NSAIDs with diuretics may increase the risk of nephrotoxicity. In patients with dehydration or hypovolaemia, NSAIDs may cause acute renal failure.

PREGNANCY AND LACTATION:

Safety during pregnancy and lactation has not been established.

FRUSEMIDE DEZZO 10 mg/ml should not be used during pregnancy and breastfeeding since it crosses the placenta and also appears in breastmilk. It may compromise placental perfusion by reducing maternal blood volume. It may also inhibit lactation.

DOSAGE AND DIRECTIONS FOR USE:

Dosage

Use the lowest dose sufficient to achieve the desired effect.

The usual dose of FRUSEMIDE DEZZO 10 mg/ml is 20 mg to 80 mg per day given as a

single dose, preferably in the morning. This dose may, however, be increased depending on the response of the patient. Six hours after a 40 mg dose, 80 mg may be administered and, if necessary, after another six hours, 120 mg. After the oedema is controlled, maintenance therapy is continued at 20 mg to 40 mg daily. Daily doses exceeding 120 mg should preferably be distributed over two to three individual doses.

Hypertension: Intravenous or intramuscular administration of FRUSEMIDE DEZZO 10 mg/ml is only indicated where intestinal absorption is impaired or prompt diuresis required. The effect produced by intravenous injection may result in a transitory fall in plasma volume.

Pulmonary oedema: Initial dose is 40 mg intravenously. If necessary, the injection may be repeated after approximately 20 minutes.

Infants and children under 15 years: Children generally receive an oral dose. Parenteral administration is indicated only in life-threatening conditions. In this case, infants/children receive parenteral doses of 1 mg/kg body mass per day up to a maximum of 20 mg per day, as continuous drip infusion.

Directions for Use

Intravenous or intramuscular administration is indicated only in cases where intestinal absorption is impaired or more rapid fluid elimination is necessary.

Intravenously, FRUSEMIDE DEZZO 10 mg/ml should be injected or infused slowly. The rate of injection of 4 mg per minute should not be exceeded. Transfer to oral therapy should be carried out as soon as possible.

During long-term treatment, serum creatinine and urea and also electrolytes, in particular

potassium, calcium, chloride and bicarbonate should be regularly checked.

In patients with severe renal function impairment, an infusion rate of 2,5 mg/min should not be exceeded.

Compatibility

FRUSEMIDE DEZZO 10 mg/ml should not be mixed with other medicines in the same injection needle.

FRUSEMIDE DEZZO 10 mg/ml is compatible with the following diluents for a time period of 48 hours at 25 ºC:

0,9 % sodium chloride solution, 0,9 % sodium chloride solution and 5 % dextrose solution, compound sodium lactate solution.

It is incompatible with 5 % and 10 % dextrose solutions.

SIDE-EFFECTS:

Blood and the lymphatic system disorders

Less frequent: Bone marrow depression, agranulocytosis, thrombocytopenia, leucopenia, aplastic or haemolytic anaemia, eosinophilia.

Frequency unknown: Blood coagulation disorders.

Immune system disorders

Less frequent: Hypersensitivity reactions including anaphylaxis, interstitial nephritis and vasculitis.

Metabolism and nutrition disorders

Frequent: Fluid and electrolyte imbalance (signs include: dry mouth, thirst, weakness, lethargy, drowsiness, restlessness), hyponatraemia, hypokalaemia, hypochloraemic alkalosis, hypocalcaemia, hypomagnesaemia.

Less frequent: Hyperuricaemia, gout, hyperglycaemia, glycosuria~~.~~, increased blood creatinine, increased cholesterol and triglyceride levels.

Nervous system disorders

Frequent: Hepatic encephalopathy, paraesthesia.

Less frequent: Paraesthesia, ~~D~~dizziness, headache.

Eye disorders

Less frequent: Blurred vision, yellow vision.

Ear and labyrinth disorders

Less frequent: Tinnitus, deafness.

Cardiac disorders

Less frequent: Cardiac dysrhythmias.

Vascular disorders

188	*Frequent:* Hypotension.
189	*Less frequent:* Hypovolaemia, dehydration, orthostatic hypotension, embolism, tendency for
190	thromobosis, circulatory collapse.
191	**Gastrointestinal disorders**
192	*Frequent:* Gastrointestinal disturbances, such as nausea, vomiting, diarrhoea, acute
193	pancreatitis.
194	**Hepato-biliary disorders**
195	*Less frequent:* Cholestatic jaundice, increased liver transaminases.
196	**Skin and subcutaneous tissue disorders**
197	*Less frequent:* Skin rashes, photosensitivity reactions, itching, urticaria, erythema multiforme,
198	phemphigoid purpurea, Stephens-Johnson syndrome, toxic epidermal necrolysis.
199	**Musculoskeletal, connective tissue and bone disorders**
200	*Frequent:* Muscle cramps, tetany.
201	**Renal and urinary disorders**
202	*Less frequent:* Oliguria, interstitial nephritis, nephrocalcinosis.
203	**General disorders and administrative site conditions**
204	*Less frequent:* Fever.
205	**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**
206	The clinical picture in acute or chronic overdose depends primarily on the extent and

207 208 209 210 211 212 213 214 215 216 217	consequences of electrolyte and fluid loss, eg., hypovolaemia, dehydration, haemoconcentration, cardiac dysrhythmias due to excessive diuresis. Symptoms include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flacid paralysis, apathy and confusion. Treatment should be aimed at fluid replacement and correction of the electrolyte imbalance, in accordance with urine output (with monitoring of carbohydrate metabolism if necessary). If difficulty in micturition is proved or suspected, as in cases of prostatic hypertrophy or impairment of consciousness, care must be taken to ensure a free outflow of urine from the bladder. No specific antidote to FRUSEMIDE DEZZO 10 mg/ml is known. Treatment is symptomatic and supportive. The clearance of frusemide is not increased by haemodialysis.
218 219	**IDENTIFICATION:** A clear and colourless to almost colourless solution.
220 221 222	**PRESENTATION:** 2 ml and 5 ml amber coloured, Ph Eur Type I glass ampoules. Cartons of 5 amber glass ampoules.
223 224 225 226	**STORAGE INSTRUCTIONS:** Store at or below 30 ºC. Do not refrigerate or freeze. Keep in the outer carton until required for use in order to protect from light. KEEP OUT OF REACH OF CHILDREN.

227	**REGISTRATION NUMBER:**
228	To be allocated
229	**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF**
230	**REGISTRATION:**
231	Dezzo Trading 392 (Pty) Limited, T/A Indo Pharma
232	Cnr Birch and Bluegum Avenue
233	Anchorville
234	Lenasia
235	1827
236	**DATE OF PUBLICATION OF THE PACKAGE INSERT:**
237	To be allocated.