PROPOSED ANNOTATED PROFESSIONAL INFORMATION		
		Reference
1 2 3 4	**SCHEDULING STATUS:** S0 Pack of 20 tablets S1 Pack of 100 tablets	Medicines and related Substances Act, 1965 (Act 101 of 1965), as amended.
5 6 7	**1. NAME OF THE MEDICINE:** **[PRODUCT NAME], tablet**	[Sec. 1.2.1]
8 9 10 11 12	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION:** Each tablet contains 500 mg paracetamol. Sugar free For full list of excipients, see section 6.1	[Sec. 3.2.P.1] Professional Information Guideline 2.16_Jul19_v2
13 14 15 16 17	**3. PHARMACEUTICAL FORM** Tablet White, round, flat, beveled edge tablets, plain on one side and break line on the other side.	[Sec.3.2.P.5.1]

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18 19 20 21 22	**4. CLINICAL PARTICULARS:** **4.1 Therapeutic indications** The relief of mild to moderate pain and fever such as headaches, toothache and pain associated with colds and flu.	[Ref. 1.3.1.2: std-1, page 1, line 24-26]
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	**4.2 Posology and method of administration** **<u>Posology</u>** *Children 6 – 12 years:* ½ - 1 tablet every 6 hours. Not more than 4 doses to be taken in any24-hour period. *Children over 12 years:* 1 tablet every 4 – 6 hours. Not more than 4 tablets to be taken in any 24-hour period. *Adults:* 1 – 2 tablets every 4 – 6 hours. Not more than 8 tablets to be taken in any 24-hour period. **DO NOT EXCEED THE RECOMMENDED DOSE** **Paediatric population:** *Children under 6 years:* Not recommended.	[Ref. 1.3.1.2: std-1, page 2, line 20-26]

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38 39 40 41	**<u>Method of administration</u>** [PRODUCT NAME] should be taken orally. The tablets should be swallowed with liquid and should not be chewed.	
42 43 44 45 46 47	**4.3 Contraindications** [PRODUCT NAME] is contraindicated in the following: • Hypersensitivity to paracetamol, or any of the other ingredients in [PRODUCT NAME]. • Severe liver function impairment.	[Ref. 1.3.1.2: std-1, page 1, line 29-32]
48 49 50 51 52 53 54 55 56 57	**4.4 Special warnings and precautions for use** • Consult a doctor or pharmacist if pain or fever persists or gets worse at the recommended dosage, or if new symptoms occur. • Do not use [PRODUCT NAME] continuously without consulting a medical practitioner: Pain – for more than 7 days in adults (5 days for children); and Fever – for more than 3 days. • Dosages in excess of those recommended may cause	

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58	severe liver damage.	
59	• Patients suffering from hepatitis or alcoholism, or	
60	recovering from any form of liver disease should not take	
61	excessive quantities of [PRODUCT NAME].	
62	• Caution is recommended in patients with moderate renal	
63	failure and patients on dialysis, as plasma concentrations	
64	of [PRODUCT NAME] and its conjugates are increased.	[Ref. 1.3.1.2: std-1, Page 1, line 34-44]
65	• Use with caution in renal impairment, chronic	
66	malnutrition or dehydration.	
67	• Caution should be exercised in patients with glutathione	
68	depleted states, as the use of paracetamol may increase	
69	the risk of metabolic acidosis.	[Ref. 1.3.1.2: std-2, age 1, line 35-37]
70	• Use with caution in patients with glutathione depletion	
71	due to metabolic deficiencies.	
72	[PRODUCT NAME] contains paracetamol which may be fatal	
73	in overdose. In the event of overdosage or suspected	[Ref. 1.3.1.2: std-1, Page 1, line 45-47]
74	overdose and notwithstanding the fact that the person may be	
75	asymptomatic, the nearest doctor, hospital or Poison Centre	
76	must be contacted immediately.	
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79	**4.5 Interaction with other medicines and other forms of**	
80	**interaction**	
81	*Hepatotoxic medicines:* Increased risk of hepatotoxicity.	
82	*Enzyme-inducing medicines:* Increased risk of hepatotoxicity	[Ref. 1.3.1.2: std-1, Page 1, line 49]
83	and possible decrease in therapeutic effects of [PRODUCT	
84	NAME].	
85	*Metoclopramide:* Absorption of [PRODUCT NAME] may be	
86	accelerated.	
87	*Probenecid:* Pre-treatment with probenecid can decrease	
88	[PRODUCT NAME] clearance, and increase its half-life.	
89	*Cholestyramine:* Absorption of [PRODUCT NAME] is reduced if	
90	given within one hour of cholestyramine.	
91	*Salicylates:* Prolonged concurrent use of [PRODUCT NAME]	
92	with salicylates increases the risk of adverse renal effects.	
93	*Antibiotics:* Chronic use of isoniazid, an antibiotic medicine often	
94	prescribed for tuberculosis, may increase the risk of liver	
95	damage when combined with [PRODUCT NAME], even at	[Ref. 1.3.1.2: std-1, Page 2, line 1-12]
96	recommended doses.	
97	*Warfarin:* The anticoagulant effect of warfarin and other	
98	coumarins may be enhanced by prolonged regular daily use of	
99	paracetamol with increased risk of bleeding; occasional doses	[Ref. 1.3.1.2: std-2, Page 2, line 3-4
100	have no significant effect.	

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102 103 104 105 106 107 108 109 110 111 112 113 114	**4.6 Fertility, pregnancy and lactation** **Pregnancy** [PRODUCT NAME] is generally considered safe for use in pregnant patients, if used infrequently (not daily or on most days). **Breastfeeding** [PRODUCT NAME] is distributed into breastmilk, in amounts too small to be considered harmful to a breast-fed infant. No significant adverse effects have been seen in breast-fed infants whose mothers received paracetamol. **Fertility** There is no data on adverse effects on male or female fertility.	[Ref. 1.3.1.2: std-1, page 2, line 13-18]
115 116 117	**4.7 Effects on ability to drive and use machines** None	[Ref. 1.3.1.2: std-2, page 2, line 11-12]
118 119	**4.8 Undesirable effects**	

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System Organ Class	Adverse reaction	Frequency	
Blood and lymphatic system disorders	Neutropenia, pancytopenia, leucopenia, thrombocytopenia, agranulocytosis	Less frequent	[Ref. 1.3.1.2: std-1, page 2, line 35-36] [Ref. 1.3.1.2: std-2, page 2, line 23-24]
Immune system disorders	Anaphylaxis. Hypersensitivity reactions (characterised by urticaria, dyspnoea and hypotension) Angioedema	Less frequent	[Ref. 1.3.1.2: std-2, page 2, line 25] [Ref. 1.3.1.2: std-1, page 2, line 33-34]
Respiratory, thoracic and mediastinal disorders	Bronchospasm	Less frequent	[Ref. 1.3.1.2: std-2, page 2, line 31-32]
Hepatobiliary disorders:	Hepatic dysfunction	Less frequent	[Ref. 1.3.1.2: std-2, page 2, line 33]
Skin and subcutaneous	Skin rashes. Skin rashes are usually	Less frequent	[Ref. 1.3.1.2: std-1, page 2, line 30-32]

143 144 145 146 147 148	**tissue disorder**	erythematous or urticarial, but sometimes more serious and may be accompanied by fever and mucosal lesions.		
149 150 151 152 153 154 155 156 157 158	**<u>Reporting of suspected adverse reactions</u>** Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Medicine Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.			Professional Information Guideline 2.16_Jul19_v2
159 160 161 162 163	**4.9 Overdose:** **Prompt treatment is essentia**l. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. A delay in starting treatment may mean that the antidote is given too late to be effective. Evidence of liver			

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164	damage is often delayed until after the time for effective	
165	treatment has lapsed.	
166	Susceptibility to paracetamol toxicity is increased in patients	
167	who have taken repeated high doses (greater than 5 – 10 g/day)	
168	of paracetamol for several days, in chronic alcoholism, chronic	
169	liver disease, AIDS, malnutrition, and with the use of medicines	
170	that induce liver microsomal oxidation such as barbiturates,	
171	isoniazid, rifampicin, phenytoin and carbamazepine.	
172	Symptoms of paracetamol overdosage in the first 24 hours	
173	include pallor, nausea, vomiting, anorexia and possibly	
174	abdominal pain. Mild symptoms during the first two days of	
175	acute poisoning, do not reflect the potential seriousness of the	
176	overdosage.	
177	Liver damage may become apparent 12 to 48 hours, or later	
178	after ingestion, initially by elevation of the serum transaminase	
179	and lactic dehydrogenase activity, increased serum bilirubin	
180	concentration and prolongation of the prothrombin time. Liver	
181	damage may lead to encephalopathy, coma and death.	
182	Acute renal failure with acute tubular necrosis may develop even	
183	in the absence of severe liver damage. Abnormalities of glucose	
184	metabolism and metabolic acidosis may occur. Cardiac	
185	arrhythmias have been reported.	

After maternal overdosage during pregnancy, foetal metabolism of paracetamol that crosses the placenta can produce hepatotoxic metabolites, causing foetal hepatotoxicity.

Treatment for paracetamol overdosage:

Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

IV: An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given **intravenously** over 15 minutes,

followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children.**

Oral: Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading.

Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below.

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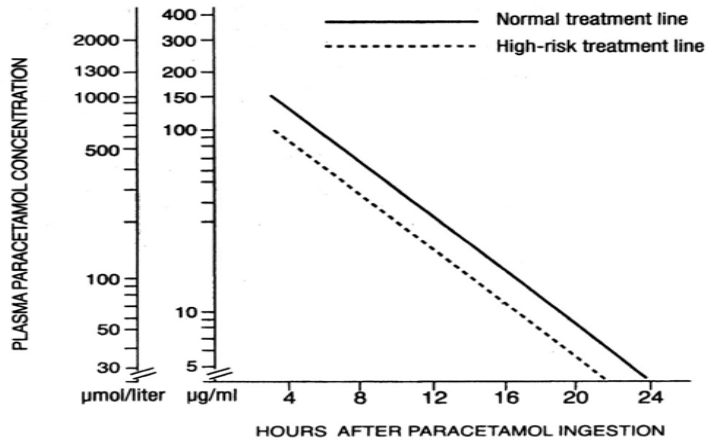

** Nomogram reproduced from the Guidelines for the Management of Acute Paracetamol Overdose produced by the Medicines Information Centre, UCT.*

The nomogram should be used only in relation to a single acute ingestion. Those, whose plasma paracetamol levels are above the "normal treatment line", should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the "high risk treatment line" (*refer to paracetamol nomogram above)*. Prothrombin index correlates best with survival.

Monitor all patients with significant ingestions for at least ninety-six hours.

[Ref. 1.3.1.2: std-1, page 2, line 38-53, page 3, line 1-37]

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	Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours. In most cases hepatic transaminases return to normal in one to two weeks with full restitution of the liver function. In very severe cases, however, liver transplantation may be necessary.	
252 253 254 255 256 257 258 259	**5. PHARMACOLOGICAL PROPERTIES** **5.1 Pharmacodynamic properties** Pharmacological classification: A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics ATC Code: N02BE01 Paracetamol has analgesic and antipyretic activity.	[Ref. 1.3.1.2: std-1, page 1, line 12-15]
260 261 262 263 264 265	**5.2 Pharmacokinetic properties** **Absorption:** Paracetamol is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring approximately 10 – 60 minutes after oral doses. **Distribution:**	

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266	Paracetamol is distributed into most body tissues. It crosses	
267	the placenta and is present in breast milk.	
268	**Biotransformation:**	
269	Paracetamol is mainly metabolised in the liver, following two	
270	major hepatic pathways: glucuronic acid conjugation and	
271	sulphuric acid conjugation.	
272	**Elimination:**	
273	The metabolites of paracetamol are mainly excreted in the	
274	urine. Less than 5 % is excreted as unchanged paracetamol.	
275	The elimination half-life of paracetamol varies from about 1 – 3	[Ref. 1.3.1.2: std-1, page1, line 16-23]
276	hours.	
277		
278	**5.3 Preclinical safety data**	
279	Conventional studies using the currently accepted standards	[Ref. 1.3.1.2: std-2, page 3, line 35-36]
280	for the evaluation of toxicity to reproduction and development	
281	are not available.	
282		
283	**6 PHARMACEUTICAL PARTICULARS**	
284	**6.1 List of excipients**	[Sec.3.2.P.1]
285	Colloidal anhydrous silica, dioctyl sodium sulphosuccinate,	
286	magnesium stearate, maize starch, polyvinylpyrrolidone	

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288 289 290	**6.2 Incompatibilities** Not applicable	
291 292 293	**6.3 Shelf life** 4 years (proposed)	[Sec. 3.2.P.8.1]
294 295 296 297 298 299	**6.4 Special precautions for storage** Store at or below 30 °C. Protect from light and moisture. Store in the original package/container. Keep the blister in the carton until required for use	[Sec. 3.2.P.8]
300 301 302 303 304	**6.5 Nature and contents of container** [PRODUCT NAME] is packed in a blister comprising of plain aluminium foil with VMCH coating and clear transparent PVC film and placed in a preprinted carton along with a patient information leaflet.	[Sec.3.2.P.7]

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305 306 307	Pack sizes: 20 and 100 tablets Not all pack sizes may be marketed.	
308 309 310	**6.6 Special precautions for disposal** No special requirements.	
311 312 313 314 315 316 317 318 319	**7 HOLDER OF CERTIFICATE OF REGISTRATION** Oethmaan Biosims (Pty) Ltd 207A Sherwood House Greenacres Office Park c/o Victory and Rustenberg Roads Victory Park Johannesburg 2195	
320 321 322	**8 REGISTRATION NUMBER(S):** To be allocated	

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323 324 325	**9 DATE OF FIRST AUTHORISATION** Date of registration: To be advised	
326 327 328	**10 DATE OF REVISION OF THE TEXT** Not applicable	