PROPOSED ANNOTATED PROFESSIONAL INFORMATION		
		Reference
1 2	**SCHEDULING STATUS:** S5	Medicines and related Substances Act, 1965 (Act 101 of 1965), as amended.
3 4 5	**1. NAME OF THE MEDICINE:** **[PRODUCT NAME], film-coated tablet**	[Sec. 1.2.1]
6 7 8 9 10 11 12	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION:** Each film-coated tablet contains 37,5 mg tramadol hydrochloride and 325 mg paracetamol as the active ingredients. 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** Film-coated tablet. Light yellow, oblong, biconvex, film-coated tablets, plain on both sides.	[Sec.3.2.P.5.1]

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18 19 20 21 22 23 24	**4. CLINICAL PARTICULARS:** **4.1 Therapeutic indications** [PRODUCT NAME] is indicated for the management of moderate to moderately-severe pain in adults. [PRODUCT NAME] is not recommended for minor pain that may be treated adequately through lesser means.	[Ref. 1.3.1.2: std-1, page 2, line 14-15]
25 26 27 28 29 30 31 32 33 34 35 36 37	**4.2 Posology and method of administration** **<u>Posology</u>** To be used in adults and children over 16 years of age. **DO NOT EXCEED THE RECOMMENDED DOSE**. **Adults** For the management of pain, the recommended dose of [PRODUCT NAME] is 1 or 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. As with all analgesic medicines, a titration period of several days with gradual dose increases at the initiation of [PRODUCT NAME] therapy may be beneficial for some patients. Clinical studies with tramadol in patients with moderate to moderately severe chronic pain indicate that the	

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38 39 40 41 42 43 44 45 46 47 48 49 50	tolerability of tramadol can be improved by starting tramadol at a low dose with gradual upward dose titration to reach doses that provide sufficient pain relief. **Special populations**: **Renal impairment** For patients with creatinine clearance < 30 mL/min, the dosing interval of [PRODUCT NAME] should be increased not to exceed 2 tablets every to 12 hours. **Paediatric population:** Safety and efficacy in children have not been established.	[Ref. 1.3.1.2: std-1, page 7, line 8-20]
51 52 53 54	**<u>Method of administration</u>** [PRODUCT NAME] should be taken orally. The tablets should be swallowed with liquid and should not be chewed.	
55 56 57 58	**4.3 Contraindications** [PRODUCT NAME] is contraindicated in patients with a known hypersensitivity to tramadol, paracetamol or other opioids such as codeine.	

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59 60 61 62 63 64 65 66 67 68 69 70 71 72 73	It is also contraindicated in cases of severe liver function impairment and in acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines. It should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal. [PRODUCT NAME] must not be used for narcotic withdrawal treatment. [PRODUCT NAME] should not be given to patients with respiratory depression especially in the presence of cyanosis and excessive bronchial secretions. [PRODUCT NAME] should not be given to patients with increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.	[Ref. 1.3.1.2: std-1, page 2, line 17-22] [Ref. 1.3.1.2: std-1, page 3, line 1-5]
74 75 76 77 78 79	**4.4 Special warnings and precautions for use** **This product contains paracetamol, which may be fatal in overdose.** **In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison**	

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80	**Centre must be contacted immediately.**	
81		
82	Dosages in excess of those recommended may cause severe	
83	liver damage. Patients suffering from liver or kidney disease	
84	should take paracetamol containing medicines under medical	
85	supervision.	
86	Tramadol may only be taken with special care in opioid	
87	dependence, reduced level of consciousness of uncertain	
88	origin, disorders of the respiratory function and increased	
89	intracranial pressure.	
90		
91	**Seizures:**	
92	Seizures have been reported in patients receiving tramadol at	
93	dosages within the recommended dosage range. The risk of	
94	seizures is enhanced in patients exceeding the recommended	
95	dose, or in patients taking tricyclic anti-depressants or other	
96	tricyclic compounds e.g. promethazine, selective serotonin	
98	reuptake inhibitors, MAO-inhibitors and neuroleptics. The risk	
99	of seizures may also be increased in patients with epilepsy,	
100	with a history of seizures or in patients with a recognised risk	
101	for seizures e.g. drug and alcohol withdrawal, intracranial	
102	infections, head trauma, metabolic disorders and naloxone	

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103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124	administration with tramadol overdose. Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with tramadol. **CYP2D6 ultra-rapid metabolism of tramadol:** Patients who are CYP2D6 ultra-rapid metabolisers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may lead to higher than expected serum M1 levels which could lead to an increased risk of respiratory depression. Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolisers. **Drug Abuse and Dependence:** Tramadol has a dependence potential and tolerance, psychic and physical dependence of the morphinetype (μ opioid) may develop with long-term use. The medicine has been associated with craving, drug-seeking behaviour and tolerance development. Cases of abuse and dependence on tramadol have been reported. Tramadol should not be used in opioid-	[Ref. 1.3.1.2: std-1, page 3. Line 6-21]

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125 dependent patients. Tramadol can reinstate physical 126 dependence in patients that have been previously dependent 127 or chronically using other opioids. In patients with a tendency to 128 drug abuse, a history of drug dependence or who are 129 chronically using opioids, treatment with tramadol is not 130 recommended.		
131		
132 **Withdrawal:**		
133 Withdrawal symptoms may occur if [PRODUCT NAME] is 134 discontinued abruptly. Panic attacks, severe anxiety, 135 hallucinations, paraethesia, tinnitus, and unusual CNS 136 symptoms have also been reported with abrupt discontinuation 137 of tramadol hydrochloride. Clinical experience suggests that 138 withdrawal symptoms may be relieved by tapering the 139 medication.		
140		
141 **Serious skin reactions:**		
142 Serious skin reactions such as acute generalised 143 exanthematous pustulosis (AGEP), Stevens-Johnson 144 syndrome (SJS), and toxic epidermal necrolysis (TEN), have 145 been reported in patients receiving paracetamol. Patients 146 should be informed about the signs of serious skin reactions,		[Ref. 1.3.1.2: std-1, page 4. Line 1-21]

PROPOSED ANNOTATED PROFESSIONAL INFORMATION		
147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168	and use of [PRODUCT NAME] should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity. **Precautions – general:** Do not co-administer [PRODUCT NAME] with other tramadol or paracetamol containing medicines. **Use with alcohol:** [PRODUCT NAME] should not be taken with alcohol containing beverages. **Use with CNS depressants:** The administration of [PRODUCT NAME] concurrently with central nervous system (CNS) depressants such as alcohol, opioids, anaesthetic agents, phenothiazines, tranquilisers or sedative hypnotics is likely to intensify and prolong CNS effects. **Use in renal disease:** [PRODUCT NAME] should be used with caution in patients with impaired renal function and in patients prone to convulsive	

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169	disorders or in shock.	
170		
171	**Hyponatraemia:**	
172	Hyponatraemia has been reported with the use of [PRODUCT	
173	NAME], usually in patients with predisposing risk factors, such	
174	as elderly patients and/or patients using concomitant	
175	medications that may cause hyponatraemia. This	
176	hyponatraemia appeared to be the result of the syndrome of	
177	inappropriate antidiuretic hormone secretion (SIADH) and	
178	resolved with discontinuation of [PRODUCT NAME] and	[Ref. 1.3.1.2: std-1,
179	appropriate treatment (e.g. fluid restriction). During [PRODUCT	page 5. Line 1-21]
180	NAME] treatment, monitoring for signs and symptoms of	
181	hyponatraemia is recommended for patients with predisposing	
182	risk factors.	
183		
184	**Sleep-related breathing disorders**	
185	Opioids can cause sleep-related breathing disorders including	[Ref. 1.3.1.2: std-2,
186	central sleep apnoea (CSA) and sleep-related hypoxemia.	page 2. Line 33-36]
187	Opioid use increases the risk of CSA in a dose-dependent	
188	fashion. In patients who present with CSA, consider decreasing	
189	the total opioid dosage.	
190		

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191 192 193 194 195 196	**Use in general anaesthesia** In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.	[Ref. 1.3.1.2: std-2, page 3. Line 3-5]
197 198 199 200 201 202 203 204 205 206 207 208 209 210 211	**4.5 Interaction with other medicinal products and other forms of interaction** [PRODUCT NAME] must not be combined with a MAO-inhibitor, or within 14 days of discontinuation of it, as potentiation of serotonergic and noradrenergic effects may result (see Section 4.3). Concomitant administration of [PRODUCT NAME] and carbamazepine may cause significantly decreased tramadol and M1 concentrations. Patients receiving carbamazepine may have significantly reduced analgesic effect from the tramadol component of [PRODUCT NAME]. Concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, quinidine and amitriptyline could result in	

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212	some inhibition of the metabolism of tramadol.	
213		
214	Simultaneous administration with cimetidine is associated with	
215	clinically insignificant changes in serum concentrations of	
216	tramadol. Therefore, no alteration of the [PRODUCT NAME]	
217	dosage regimen is recommended for patients receiving chronic	
218	cimetidine therapy.	
219		
220	Post-marketing surveillance of tramadol has revealed rare	
221	reports of digoxin toxicity and rare alterations of warfarin effect	
222	including elevation of prothrombin times.	
223	Periodic evaluation of prothrombin time / INR should be	
224	performed when [PRODUCT NAME] is administered	
225	concurrently with warfarin like compounds, due to reports of	[Ref. 1.3.1.2: std-1, page 6, line 5-19]
226	increased prothrombin time / INR in some patients.	
227		
228	Concomitant administration of diflunisal and paracetamol	
229	produces a 50 % increase in paracetamol plasma levels in	[Ref. 1.3.1.2: std-1, page 7, line 1-3]
230	normal volunteers. [PRODUCT NAME] should be used	
231	cautiously and patients should be monitored carefully.	
232		
233	**Concomitant use is not recommended with**:	

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234	• **Alcohol** Alcohol increases the sedative effect of opioid analgesics. The effect on alertness can make driving of vehicles and the use of machines dangerous. Avoid intake of alcoholic drinks and of medicines containing alcohol.	
242	• **Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)** Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.	
248	**Concomitant use which needs to be taken into consideration:** • Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs) serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and seizure threshold lowering medicines (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause	

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256	convulsions.	
257		
258	• Concomitant therapeutic use of tramadol and	
259	serotonergic medicines such as selective serotonin re-	
260	uptake inhibitors (SSRIs) serotonin-norepinephrine	
261	reuptake inhibitors (SNRIs), MAO inhibitors (see section	
262	4.3), tricyclic antidepressants and mirtazapine may	
263	cause serotonin toxicity.	
264	Serotonin syndrome is likely when one of the following	
265	is observed:	
266	o Spontaneous clonus	
267	o Inducible or ocular clonus with agitation or	
268	diaphoresis	
269	o Tremor and hyperreflexia	
270	o Hypertonia and body temperature > 38 °C and	
271	inducible or ocular clonus.	
272	Withdrawal of the serotonergic medicines usually brings	
273	about a rapid improvement. Treatment depends on the	
274	type and severity of the symptoms.	
275		
276	• Other opioid derivatives (including antitussive	
277	medicines and substitutive treatments).	

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278	Increased risk of respiratory depression which can be	
279	fatal in cases of overdose.	
280		
281	• Other central nervous system depressants, such as	
282	other opioid derivatives (including antitussive medicines	
283	and substitutive treatments), other anxiolytics,	
284	hypnotics, sedative antidepressants, sedative	
285	antihistamines, neuroleptics, centrally-acting	
286	antihypertensive medicines, thalidomide and baclofen.	[Ref. 1.3.1.2: std-2, page 3, line 20-50]
287	These medicines can cause increased central	
288	depression. The effect on alertness can make driving of	
289	vehicles and the use of machines dangerous.	
290		
291	• Sedating medicines such as benzodiazepines or related	
292	substances:	
293	The concomitant use of opioids with sedative medicines	
294	such as benzodiazepines or related medicines	
295	increases the risk of sedation, respiratory depression,	
296	coma and death because of additive CNS depressant	
297	effects. The dose and duration of the concomitant use	
298	should be limited (see section 4.4).	
299		

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300 301 302 303 304	• In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.	[Ref. 1.3.1.2: std-2, page 4, line 1-8]
305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320	**4.6 Fertility, pregnancy and lactation** Safe use in pregnancy and lactation has not been established. [PRODUCT NAME] is not recommended for pregnant mothers because tramadol has been shown to cross the placenta. ***Pregnancy*** Since [PRODUCT NAME] is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy. • Data regarding paracetamol: Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosages. • Data regarding tramadol: Tramadol should not be used during pregnancy as there is inadequate evidence available to assess the	[Ref. 1.3.1.2: std-1, page 7, line 5-6]

safety of tramadol in pregnant women. Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation.

Breastfeeding:

Since [PRODUCT NAME] is a fixed combination of active ingredients including tramadol, it should not be ingested during breastfeeding.

- Data regarding paracetamol:

  Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding by women using single ingredient medicines containing only paracetamol.

- Data regarding tramadol:

  Approximately 0.1 % of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by

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343 344 345 346 346 348 349 350 351 352 353 354 355	breast-fed infants of 3 % of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breastfeeding should be discontinued during treatment with tramadol. Discontinuation of breastfeeding is generally not necessary following a single dose of tramadol. ***Fertility*** Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of tramadol and paracetamol.	[Ref. 1.3.1.2: std-2, page 4, line 10-36]
356 357 358 359 360 361	**4.7 Effects on ability to drive and use machines** [PRODUCT NAME] may affect reactions to the extent that driving ability and the ability to operate machinery may be impaired. This applies particularly in conjunction with other psychotropic medicines including alcohol.	[Ref. 1.3.1.2: std-1, page 6, line 1-3]
362	**4.8 Undesirable effects**	

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System Organ Class	Adverse reaction	Frequency	
Blood and lymphatic system disorders	Anaemia	Less frequent	[Ref. 1.3.1.2: std-1, page 9, line 15]
Immune system disorders	Hypersensitivity reactions including anaphylaxis	Less frequent	[Ref. 1.3.1.2: std-1, page 10, line 7]
Metabolism and nutrition disorders	Weight decrease Hypoglycaemia	Less frequent	[Ref. 1.3.1.2: std-1, page 9, line 5] [Ref. 1.3.1.2: std-1, page 10, line 15]
Psychiatric disorders	Anorexia, anxiety, confusion, euphoria, insomnia, nervousness	Frequent	
	Amnesia, depersonalisation, depression, drug abuse, emotional lability, hallucination, impotence, bad dreams, abnormal thinking	Less frequent	[Ref. 1.3.1.2: std-1, page 9, line 8-14]

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	Cognitive dysfunction, suicidal tendency	Frequency unknown	[Ref. 1.3.1.2: std-1, page 10, line 8]
Nervous system disorders	Dizziness, somnolence, headache, tremor	Frequent	
	Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo	Less frequent	[Ref. 1.3.1.2: std-1, page 8, line 18-23]
	Delirium, speech disorder	Frequency unknown	[Ref. 1.3.1.2: std-1, page 10, line 13]
Eye disorders:	Abnormal vision	Less frequent	[Ref. 1.3.1.2: std-1, page 9, line 22]
	Miosis, mydriasis	Frequency unknown	[Ref. 1.3.1.2: std-1, page 10, line 13]
Ear and labyrinth disorders	Tinnitus	Less frequent	[Ref. 1.3.1.2: std-1, page 9; line 2]

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Cardiac disorders	Dysrhythmia, palpitation, tachycardia	Less frequent	[Ref. 1.3.1.2: std-1, page 8, line 14-15]
Vascular disorders	Hypertension, aggravated hypertension, hypotension	Less frequent	[Ref. 1.3.1.2: std-1, page 8, line 12-13]
	Orthostatic hypotension	Frequency unknown	[Ref. 1.3.1.2: std-1, page 10, line 7]
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Less frequent	[Ref. 1.3.1.2: std-1, page 9, line 17]
Gastrointestinal disorders	Nausea, abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, vomiting, dry mouth	Frequent	[Ref. 1.3.1.2: std-2, page 5, line 18-19]
	Dysphagia, melaena, tongue oedema	Less frequent	[Ref. 1.3.1.2: std-1, page 8, line 24-25]
Hepatobiliary disorders:	Liver test abnormalities	Less frequent	[Ref. 1.3.1.2: std-1, page 8, line 16]

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	Hepatitis		[Ref. 1.3.1.2: std-1, page 10, line 8]
Renal and urinary disorders	Albuminuria, micturition disorder, oliguria, urinary retention	Less frequent	[Ref. 1.3.1.2: std-1, page 9, line 19-21]
Skin and subcutaneous tissue disorder	Pruritus, rash, increased sweating	Frequent	
	Urticaria, Steven Johnson Syndrome/Toxic epidermal necrolysis (TENS)	Less frequent	[Ref. 1.3.1.2: std-1, page 10, line 7-8]
General disorders and administrative site conditions	Asthenia, fatigue, hot flushes	Frequent:	[Ref. 1.3.1.2: std-1, page 10, line 1-2]
	Chest pain, rigors, syncope, withdrawal syndrome	Less frequent	
Investigations	Elevated creatinine, hyponatraemia, SIADH (Syndrome of	Frequency unknown	[Ref. 1.3.1.2: std-1, page 10, line 8-9]

	inappropriate antidiuretic hormone secretion)	
	Increased transaminases	

Serotonin syndrome (whose symptoms may include fever, excitation, shivering and agitation) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAO inhibitors. Post – marketing experience with the use of tramadol containing medicines included reports of delirium, miosis, mydriasis, and speech disorder, and reports of movement disorder. Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times. Cases of hypoglycaemia have been reported.

Cases of hyponatraemia and/or SIADH have been reported in patients taking tramadol, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medicines that may cause hyponatraemia.

[Ref. 1.3.1.2: std-1, page 10, line 16]

[Ref. 1.3.1.2: std-2, page 5, line 24]

[Ref. 1.3.1.2: std-1, page 10, line 16-18]

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473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488	Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to paracetamol are rare and generally controlled by discontinuation of the medicine, and when necessary, symptomatic treatment. There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin like compounds. In other studies, prothrombin time did not change. **<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.	[Ref. 1.3.1.2: std-1, page 11, line 3-6] Professional Information Guideline 2.16_Jul19_v2
489 490 491 492 493	**4.9 Overdose:** The clinical presentation of overdosage may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both. **Tramadol**	

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494	The initial symptoms of tramadol overdosage may include	
495	respiratory depression and/or seizures.	
496	Primary attention should be given to maintaining adequate	
497	ventilation along with general supportive treatment. While	
498	naloxone will reverse some, but not all symptoms caused by	
499	overdosage, the risk of seizures is also increased with	
500	naloxone administration. Treatment of restlessness and / or	
501	convulsions is symptomatic and supportive (benzodiazepines /	
502	barbiturates).	
503		
504	Tramadol is minimally eliminated from the serum by	
505	haemodialysis or haemofiltration. Treatment of acute	
506	intoxication with TRAMACET with haemodialysis or	
507	haemofiltration alone is therefore not suitable for detoxification.	
508		
509	**Paracetamol**	
510	**Prompt treatment is essential.** In the event of an overdosage,	
511	consult a doctor immediately, or take the person to a hospital	
512	directly. A delay in starting treatment may mean that antidote is	
513	given too late to be effective. Evidence of liver damage is often	
514	delayed until after the time for effective treatment has lapsed.	
515	Susceptibility to paracetamol toxicity is increased in patients	

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516	who have taken repeated high doses (greater than 5 -10 g/day)	
517	of paracetamol for several days, in chronic alcoholism, chronic	
518	liver disease, AIDS, malnutrition, and with the use of medicines	
519	that induce liver microsomal oxidation such as barbiturates,	
520	isoniazid, rifampicin, phenytoin and carbamazepine.	
521		
522	Symptoms of paracetamol overdosage in the first 24 hours	
523	include pallor, nausea, vomiting, anorexia and possibly	
524	abdominal pain. Mild symptoms during the first two days of	
525	acute poisoning do not reflect the potential seriousness of the	
526	overdosage.	
527		
528	Liver damage may become apparent 12 to 48 hours or later	
529	after ingestion, initially by elevation of the serum transaminase	
530	and lactic dehydrogenase activity, increased serum bilirubin	
531	concentration and prolongation of the prothrombin time. Liver	
532	damage may lead to encephalopathy, coma and death.	
533		
534	Acute renal failure with acute tubular necrosis may develop	
535	even in the absence of severe liver damage. Abnormalities of	
536	glucose metabolism and metabolic acidosis may occur.	
537	Cardiac arrhythmias have been reported.	

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538		
539	**Treatment for paracetamol overdosage:**	
540	Although evidence is limited it is recommended that any adult	
541	person who has ingested 5 - 10 grams or more of paracetamol	
542	(or a child who has had more than 140 mg/kg) within the	
543	preceding four hours, should have the stomach emptied by	
544	lavage (emesis may be adequate for children) and a single	
545	dose of 50 g activated charcoal given via the lavage tube.	
546	Ingestion of amounts of paracetamol smaller than this may	
547	require treatment in patients susceptible to paracetamol	
548	poisoning (see above). In patients who are stuperose or	
549	comatose endotracheal intubation should precede gastric	
550	lavage in order to avoid aspiration.	
551		
552	**N-acetylcysteine** should be administered to all cases of	
553	suspected overdose as soon as possible preferably within eight	
554	hours of overdosage, although treatment up to 36 hours after	
555	ingestion may still be of benefit, especially if more than 150	
556	mg/kg of paracetamol was taken. An initial dose of 150 mg/kg	
557	N-acetylcysteine in 200 mL dextrose injection given	
558	**intravenously** over 15 minutes, followed by an infusion of 50	
559	mg/kg in 500 mL dextrose injection over the next four hours,	

and then 100 mg/kg in 1000 mL dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children**.

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

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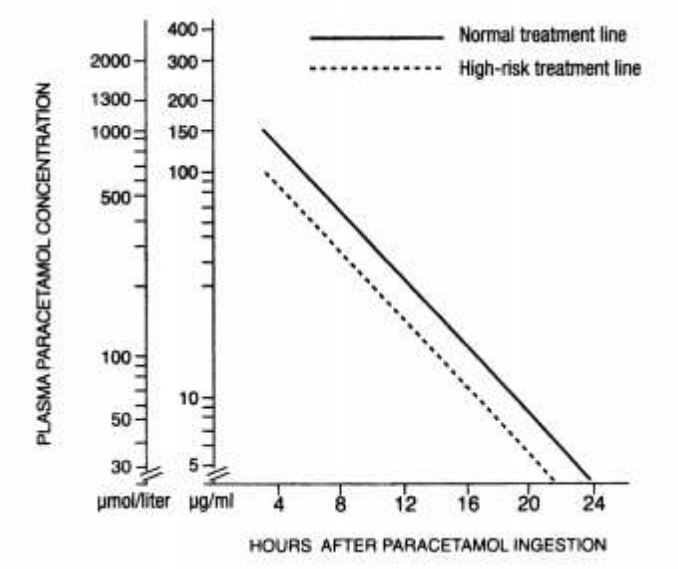
576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595	 Source: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed. Those whose plasma paracetamol levels are above the "normal treatment line", should continue N-acetylcysteine treatment with 100 mg/kg IV over 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". 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 11, line 8-22, page 12, line 1-23, page 13, line 1-14, page 14, line 1-3]

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596	**5. PHARMACOLOGICAL PROPERTIES**	
597	**5.1 Pharmacodynamic properties**	
598	Pharmacological classification: A.2.9. Other analgesics	[Ref. 1.3.1.2: std-1, page 1, line 11]
599	ATC Code: N02A J 13	
600	Tramadol is a centrally acting synthetic analgesic compound	
601	whose analgesic profile can be attributed to the binding of	
602	parent and O-demethylated (M1) metabolite to μ-opioid	
603	receptors as well as the weak inhibition of neuronal re-uptake	
604	of noradrenaline and serotonin. Paracetamol also has centrally	[Ref. 1.3.1.2: std-1, page 1, line 14-17]
605	acting analgesic effects.	
606		
607	**5.2 Pharmacokinetic properties**	
608	**Absorption:**	
609	Tramadol is well absorbed after oral administration, reaching	
610	peak activity in 2 to 3 hours. The mean absolute bioavailability	
611	of a single 100 mg oral dose is approximately 75 %, increasing	
612	to approximately 90 % with multiple dosing. Oral absorption of	
613	paracetamol following administration of TRAMACET gives a	[Ref. 1.3.1.2: std-1, page 1, line 20-21, page 2, line 1-3]
614	peak plasma concentration of paracetamol within one hour and	
615	is not affected by co-administration with tramadol.	
616	**Distribution:**	

PROPOSED ANNOTATED PROFESSIONAL INFORMATION		
617	Tramadol has a high tissue affinity (Vd,~=203 ± 40 l). It has a	
618	plasma protein binding of about 20 %.	
619	Paracetamol appears to be widely distributed throughout most	
620	body tissues except fat. Its apparent volume of distribution is	
621	about 0.9 l/kg. A relative small portion (-20 %) of paracetamol	[Ref. 1.3.1.2: std-2, page8, line 1-4]
622	is bound to plasma proteins.	
623	**Biotransformation:**	
624	Tramadol and paracetamol are both extensively metabolised in	
625	the liver.	
626	**Elimination:**	
627	Approximately 30 % of tramadol is excreted unchanged in the	
628	urine. Tramadol and its metabolites are eliminated primarily by	
629	the kidneys. The plasma elimination half-lives of tramadol and	
630	its M1 metabolite are approximately 6 and 7 hours respectively.	
631	Paracetamol is eliminated from the body primarily by formation	
632	of glucuronide and sulfate conjugates in a dose-dependent	
633	manner. The half-life of paracetamol is about 2-3 hours in	[Ref. 1.3.1.2: std-1, page 2, line 4-12]
634	adults. Less than 9 % of paracetamol is excreted unchanged in	
635	the urine.	
636		
637	**5.3 Preclinical safety data**	
638	No preclinical study has been performed with the fixed	

combination (tramadol and paracetamol) to evaluate its carcinogenic or mutagenic effects or its effects on fertility.

No teratogenic effect that can be attributed to the medicine has been observed in the progeny of rats treated orally with the combination tramadol/paracetamol.

The combination tramadol/paracetamol has proven to be embryotoxic and foetotoxic in the rat at matemo-toxic dose (50/434 mg/kg tramadol/paracetamol), i.e., 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe matemo-toxic effect (10/87 and 25/217 mg/kg tramadol/paracetamol) did not result in toxic effects in the embryo or the foetus.

Results of standard mutagenicity tests did not reveal a potential genotoxic risk for tramadol in man.

Results of carcinogenicity tests do not suggest a potential risk of tramadol for man.

Animal studies with tramadol revealed, at very high doses, effects on organ development, ossification and neonatal mortality, associated with matemotoxicity. Fertility reproductive

661	performance and development of offspring were unaffected.	
662	Tramadol crosses the placenta. Male and female fertility was	
663	not affected.	
664	Extensive investigations showed no evidence of a relevant	
665	genotoxic risk of paracetamol at therapeutic (i.e. non-toxic)	
666	doses.	
667	Long-term studies in rats and mice yielded no evidence of	
668	relevant tumorigenic effects at non-hepatotoxic dosages of	[Ref. 1.3.1.2: std-2, page 8, line 24-42]
669	paracetamol.	
670	Animal studies and extensive human experience to date yield	
671	no evidence of reproductive toxicity.	
672		
673	**6 PHARMACEUTICAL PARTICULARS**	
674	**6.1 List of excipients**	
675	Magnesium stearate, maize starch, microcrystalline cellulose,	
676	pregelatinised starch, sodium starch glycolate, Opadry yellow	
677	coating containing hypromellose, iron oxide yellow, titanium	[Sec.3.2.P.1]
678	dioxide and triacetin.	
679		

PROPOSED ANNOTATED PROFESSIONAL INFORMATION		
680 681 682	**6.2 Incompatibilities** Not applicable	
683 684 685	**6.3 Shelf life** 3 years (proposed)	[Sec. 3.2.P.8.1]
686 687 688 689 690 691	**6.4 Special precautions for storage** Store at or below 25 °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]
692 693 694 695 696 697	**6.5 Nature and contents of container** [PRODUCT NAME] is packed in a blister comprising of plain aluminium foil with VMCH coating and white opaque PVC film or in a blister comprising of plain aluminium foil with VMCH coating and white opaque PVC/PVdC film placed in a carton along with a patient information leaflet.	[Sec.3.2.P.7]

PROPOSED ANNOTATED PROFESSIONAL INFORMATION		
698 699 700	Pack sizes: 30 and 60 tablets Not all pack sizes may be marketed.	
701 702 703	**6.6 Special precautions for disposal** No special requirements.	
704 705 706 707 708 709 710 711 712	**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	
713 714 715	**8 REGISTRATION NUMBER(S):** To be allocated	

PROPOSED ANNOTATED PROFESSIONAL INFORMATION		
716 717 718	**9 DATE OF FIRST AUTHORISATION** Date of registration: To be advised	
719 720	**10 DATE OF REVISION OF THE TEXT** Not applicable	