PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

TRAPACETOL film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 37,5 mg tramadol hydrochloride and 325 mg paracetamol.

TRAPACETOL is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

TRAPACETOL: A yellow coloured, elongated, film-coated tablet with “325” debossed on one side and “37.5” debossed on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRAPACETOL is indicated for the management of moderate to moderately-severe pain in adults.

TRAPACETOL is not recommended for minor pain that may be treated adequately through lesser means.

4.2 Posology and method of administration

Posology

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 TRAPACETOL is 1 or 2 tablets every 4 to 6 hours as needed for pain relief, up to a maximum of 8 tablets per day.

At the initiation of TRAPACETOL therapy, a titration period of several days with gradual dose increase may be beneficial for some patients. Clinical studies with tramadol in patients with moderate to moderately-severe chronic pain indicate that the 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 polulation

Renal impairment:

For patients with creatinine clearance < 30 mL/min, the dosing interval of TRAPACETOL should be increased so that it does not exceed 2 tablets every 12 hours.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to tramadol hydrochloride, paracetamol, other opioids such as codeine, or to any of the excipients listed in section 6.1.
- Acute intoxication with alcohol, hypnotics, centrally acting analgesics such as opioids or psychotropic medicines.
- Patients taking monoamine oxidase inhibitors (MAOIs) or within two weeks of their discontinuation (see section 4.5).
- Narcotic withdrawal treatment.
- Severe liver function impairment.
- Respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.
- Increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.
- Safety in pregnancy and lactation has not been established (see section 4.6).
- Epilepsy not controlled by treatment (see section 4.4).

4.4 Special warnings and precautions for use

TRAPACETOL 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 centre must be contacted immediately.

General:

Do not co-administer TRAPACETOL with other medicines containing tramadol or paracetamol (including over the counter medicines).

Do not use continuously without consulting a doctor.

Continuous or excessive use of TRAPACETOL may be harmful.

TRAPACETOL may only be taken with special care in opioid dependence, reduced level of consciousness of uncertain origin, disorders of the respiratory function and increased intracranial pressure. TRAPACETOL should not be taken with alcohol-containing beverages.

Liver problems:

Dosages in excess of the recommended daily dose may cause severe liver damage. TRAPACETOL should be used with caution and only under medical supervision in patients with impaired liver function.

TRAPACETOL should not be used in patients with severe hepatic impairment (see section 4.3). The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases prolongation of dosage interval should be carefully considered.

Seizures:

TRAPACETOL should be used with care in patients with a history of epilepsy or those susceptible to seizures.

Seizures have been reported in patients receiving TRAPACETOL at dosages within the recommended dosage range. Patients exceeding the recommended dose or in patients taking tricyclic antidepressants or other tricyclic compounds such as promethazine, selective serotonin reuptake

inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and neuroleptics have an increased risk of seizures. Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with TRAPACETOL.

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 medicine, dose reduction and/or increased monitoring of signs of tramadol overdose, such as respiratory depression, is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Abuse and dependence:

Tramadol as in TRAPACETOL has a dependence potential and tolerance, psychic and physical dependence of the morphine-type (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 as in TRAPACETOL have been reported. TRAPACETOL should not be used in opioid-dependent patients and patients who are prone to addiction. Tramadol as in TRAPACETOL can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence or who are chronically using opioids, treatment with TRAPACETOL is not recommended.

Withdrawal:

Withdrawal symptoms may occur if TRAPACETOL is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms may occur with the abrupt discontinuation of tramadol. Clinical expereince suggests that withdrawal symptoms may be relieved by tapering the dose of TRAPACETOL.

Serious skin reactions:

Serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions, and use of TRAPACETOL should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Use with CNS depressants:

The administration of TRAPACETOL concurrently with central nervous system (CNS) depressants such as alcohol, opioids, anaesthetics, phenothiazines, tranquillisers or sedative hypnotics is likely to intensify and prolong CNS effects.

Use in renal disease:

TRAPACETOL should be used with caution in patients with impaired renal function and in patients prone to convulsive disorders or in shock.

Hyponatraemia:

Hyponatraemia has been reported with the use of TRAPACETOL, usually in patients with predisposing risk factors, such as eldelry patients and/or patients using concomitant medicine that may cause hyponatraemia. This hyponatraemia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of TRAPACETOL and appropriate treatment (e.g. fluid restriction). During TRAPACETOL treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use is contraindicated with:

- *Monoamine oxidase inhibitors (MAOIs):* TRAPACETOL must not be combined with a monoamine oxidase inhibitor (MAOI) or within 14 days of discontinuation thereof, as potentiation of serotonergic and noradrenergic effects may result (see section 4.3).

Concomitant use is not recommended with:

- *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.
- *Carbamazepine:* Serum concentrations of tramadol as in TRAPACETOL are reduced by carbamazepine, resulting in diminished analgesic activity from the tramadol component of TRAPACETOL.

- *Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine):* The analgesic effect is decreased due to the competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.

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 convulsions.
- Concomitant therapeutic use of tramadol and serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed:
  - Spontaneous clonus.
  - Inducible or ocular clonus with agitation or diaphoresis.
  - Tremor and hyperreflexia.
  - Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

  Withdrawal of the serotonergic medicnes usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.
- Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates.

Increased risk of respiratory depression which can be fatal in cases of overdose.

- Other central nervous system depressants, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally acting antihypertensive medicines and baclofen. These medicines can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
- Periodic evaluation of prothrombin time or international normalised ratio (INR) should be performed when TRAPACETOL is administered concurrently with warfarin due to reports of increased prothrombin time/INR in some patients.
- Metoclopramide and Domperidone may accelerate the absorption of paracetamol in TRAPACETOL.
- Cholestyramine reduces the absorption of TRAPACETOL.
- Concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, quinidine and amitriptyline may inhibit the metabolism of TRAPACETOL.
- Ondansetron increased the requirement of tramadol in patients with post-operative pain.
- Concomitant administration of diflunisal and paracetamol produces a 50 % increase in paracetamol plasma levels in normal volunteers. TRAPACETOL should be used cautiously, and patients should be monitored carefully.
- Digoxin toxicity may occur with concomitant use of TRAPACETOL.

4.6 Fertility, pregnancy and lactation

Pregnancy

- *Data regarding tramadol:*

  Tramadol should not be used during pregnancy as there is inadequate evidence available to assess the 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.

- *Data regarding paracetamol:*

  Results of epidemiological studies during human pregnancy did not reveal any harmful effects of paracetamol when used in the recommended dosages.

Breastfeeding

- *Data regarding tramadol:*

  Tramadol and its metabolites are found in small amounts in human breast milk. Tramadol 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.

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 carried out with the combination of tramadol and paracetamol.

4.7 Effects on ability to drive and use machines

Tramadol may cause drowsiness, somnolence or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported for the paracetamol/tramadol combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients.

Metabolism and nutrition disorders:

Frequency unknown: hypoglycaemia

Psychiatric disorders:

Frequent: confusional state, altered mood (anxiety, nervousness, euphoric mood), sleep disorders

Less frequent: depression, hallucinations, nightmares, delirium, drug dependence

Nervous system disorders:

Frequent: dizziness, somnolence, headache, trembling

Less frequent: involuntary muscular contractions, paraesthesia, amnesia, ataxia, convulsions, syncope, speech disorders

Eye disorders:

Less frequent: blurred vision, miosis, mydriasis

Ear and labyrinth disorders:

Less frequent: tinnitus

Cardiac disorders:

Less frequent: palpitations, tachycardia, dysrhythmia

Vascular disorders:

Less frequent: hypertension, hot flushes

Respiratory, thoracic and mediastinal disorders:

Less frequent: dyspnoea

Gastrointestinal disorders:

Frequent: nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal, pain, dyspepsia, flatulence

Less frequent: dysphagia, melaena

Skin and subcutaneous tissue disorders:

Frequent: hyperhidrosis, pruritus

Less frequent: skin reactions (e.g. rash, urticaria)

Renal and urinary disorders:

Less frequent: albuminuria, micturition disorders (dysuria and urinary retention)

General disorders and administration site conditions:

Less frequent: chills, chest pain

Investigations:

Less frequent: increased transaminases.

Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol or paracetamol cannot be excluded:

Tramadol

- Postural hypotension, bradycardia, collapse.
- Post-marketing surveillance has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
- allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
- changes in appetite, motor weakness and respiratory depression.
- Psychiatric side effects may occur which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually euphoric mood, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders).

- Worsening of asthma has been reported though a causal relationship has not been established.
- The following symptoms of withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

Paracetamol

- Hypersensitivity including skin rash may occur.
- There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
- There have been several reports that suggest that paracetamol may produce hypoprothrombinaemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.
- Cases of serious skin reactions have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TRAPACETOL is important. It allows continued monitoring of the benefit/risk balance of TRAPACETOL. Healthcare professionals are asked to report any suspected adverse reactions via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

Symptoms of overdose from tramadol:

On intoxication with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular, miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Symptoms of overdose from paracetamol:

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalophathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac dysrhythmias and pancreatitis have been reported.

Liver damage is possible in adults who have taken 7,5 – 10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue.

Emergency treatment:

- Transfer patient immediately to a specialised unit.
- Maintain respiratory and circulatory functions.
- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.
- Perform hepatic tests as soon as possible after overdose and repeat every 24 hours. An increase in hepatic enzymes (AST, ALT) is usually observed, which normalises after one or two weeks.
- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment of acute intoxication with tramadol/paracetamol with haemodialysis or haemofiltration alone is not suitable for detoxification.

Prompt treatment is essential. 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 antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 – 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and

with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.
Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

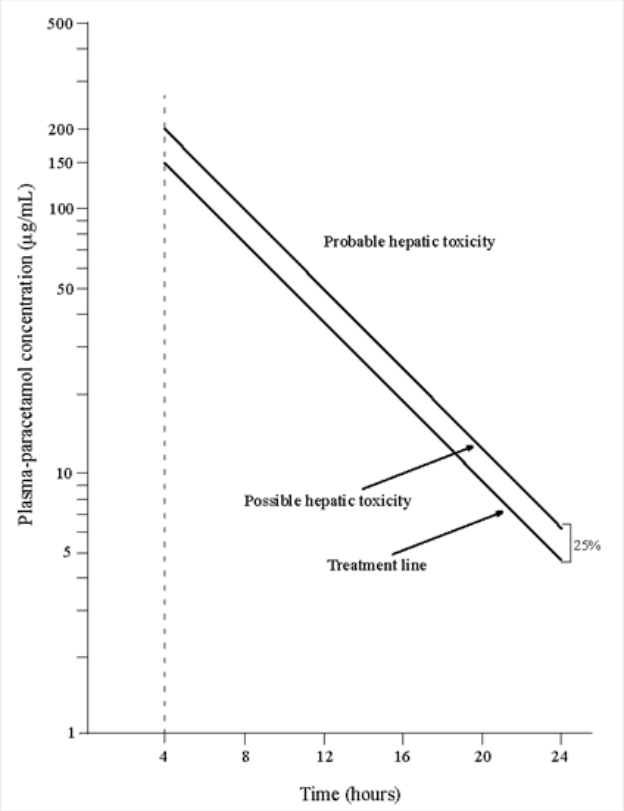
Treatment for paracetamol overdosage:

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).

***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. 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.

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. The nomogram should be used only in relation to a single acute ingestion.



A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.

Reference: Martindale The Complete Drug Reference (Online Edition).

Those whose plasma paracetamol levels are above the “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 “Possible hepatic toxicity line”. Prothrombin index correlates best with survival.

For overdose with an extended/modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such

preparations should receive *N*-acetylcysteine. Because of lack of data for extended/modified release formulations, a level below the “Treatment line” of the nomogram may not exclude the possibility of toxicity.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other opioids; Tramadol, combinations

ATC code: N02A X 52

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non-selective agonists of the μ, δ and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastrointestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

Tramadol/paracetamol is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the medical practitioner.

5.2 Pharmacokinetic properties

Tramadol is administered in racemic form and the [-] and [+] forms of tramadol and its metabolite M1, are detected in the blood. Although tramadol is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol.

After a single oral administration of a tramadol/paracetamol (37,5 mg/325 mg) tablet, peak plasma concentrations of 64,3/55,5 ng/mL [(+)-tramadol/(-)-tramadol] and 4,2 µg/mL (paracetamol) are reached after 1,8 hours [(+)-tramadol/(-)-tramadol] and 0,9 hours (paracetamol) respectively. The mean elimination half-lives $t_{½}$ are 5,1/4,7 hours [(+)-tramadol/ (-)-tramadol] and 2,5 hours (paracetamol).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of tramadol/paracetamol, no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

Absorption:

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75 %. After repeated administration, the bioavailability is increased and reaches approximately 90 %.

After administration of tramadol/paracetamol, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the

small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol. The oral administration of tramadol/paracetamol with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol, so that tramadol/paracetamol can be taken independently of meal times.

Distribution:

Tramadol has a high tissue affinity ($V_{d,\beta}$ = 203 ± 40 L). It has a plasma protein binding of about 20 %.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0,9 L/kg. A relative small portion (~20 %) of paracetamol is bound to plasma proteins.

Biotransformation:

Tramadol is extensively metabolised after oral administration. About 30 % of the dose is excreted in urine unchanged, whereas 60 % of the dose is excreted as metabolites.

Tramadol is metabolised through *O*-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1 and through *N*-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through *N*-demethylation and by conjugation with glucuronic acid. The plasma

elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect is unlikely to change on multiple dosing. Paracetamol is principally metabolised in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4 %) is metabolised by cytochrome P450 to an active intermediate (the *N*-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Elimination:

Tramadol and its metabolites are eliminated mainly by the kidneys. The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9 % of the paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

5.3 Preclinical safety data

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 fetotoxic in the rat at materno-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 fetus results in a decreased fetal mass and an increase in supernumerary ribs. Lower doses, causing less severe maternal-toxic effect (10/87 and 25/217 mg/kg tramadol/paracetamol) did not result in toxic effects in the embryo or the fetus.

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

Results of carcinogenicity tests did 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 maternal toxicity. Fertility, reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. Male and female fertility was not affected.

Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic (i.e. non-toxic) doses.

Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

Animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Purified water

Sodium starch glycolate (Type A)

Film-coating:

Hypromellose 3cP (HPMC 2910)

Hypromellose 6cP (HPMC 2910)

Iron oxide yellow)

Macrogol (PEG 400)

Polysorbate 80

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

Store at or below 25 °C, protected against moisture.

Store in original packaging and keep blisters in the outer carton until required for use.

6.5 Nature and contents of container

Pack sizes of 20, 30 or 60 film-coated tablets packed in blister strips of aluminium foil and white opaque PVC-PVdC film packed in an outer unit carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBER

51/2.9/0438

9. DATE OF FIRST AUTHORISATION

24 January 2022

10. DATE OF REVISION OF THE TEXT