Applicant: Oethmaan Biosims (Pty) Ltd	**SAHPRA approval date:** 16 August 2023
Product: OZTRAK 37.5/325	**Dosage form and strength:** Each film-coated tablet contains: 37,5 mg tramadol and 325 mg paracetamol

APPROVED PROFESSIONAL INFORMATION – CLEAN COPY

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

OZTRAK 37.5/325, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

OZTRAK 37.5/325:

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

Excipients with known effect:

OZTRAK 37.5/325 contains 0,56 mg sodium per tablet.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Light yellow, oblong, biconvex, film-coated tablets, plain on both sides.

Initial: 16/08/2023

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

OZTRAK 37.5/325 is indicated for the management of moderate to moderately-severe pain in adults.

OZTRAK 37.5/325 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 OZTRAK 37.5/325 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 OZTRAK 37.5/325 therapy 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 populations

Renal impairment:

For patients with creatinine clearance < 30 mL/min, the dosing interval of OZTRAK 37.5/325 should be increased not to exceed 2 tablets every to 12 hours.

Method of administration

For oral use.

Tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

4.3 Contraindications

- OZTRAK 37.5/325 is contraindicated in patients with a known hypersensitivity to tramadol, paracetamol, or any of the other ingredients mentioned in section 6.1 or other opioids such as codeine.
- OZTRAK 37.5/325 is also contraindicated in cases of severe liver function impairment and in acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines.
- OZTRAK 37.5/325 should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

- OZTRAK 37.5/325 must not be used for narcotic withdrawal treatment.
- OZTRAK 37.5/325 should not be given to patients with respiratory depression especially in the presence of cyanosis and excessive bronchial secretions.
- OZTRAK 37.5/325 should not be given to patients with increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.
- OZTRAK 37.5/325 is contraindicated in epilepsy not controlled by treatment.

4.4 Special warnings and precautions for use

The maximum dose of 8 tablets of Tramadol hydrochloride/Paracetamol should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a medical practitioner. (See section 4.9)

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.

Dosages in excess of those recommended may cause severe liver damage. Patients suffering from liver or kidney disease should take paracetamol containing medicines under medical supervision.

Tramadol 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.

Seizures:

Seizures have been reported in patients receiving tramadol at dosages within the recommended dosage range. The risk of seizures is enhanced in patients exceeding the recommended dose, or in patients taking tricyclic anti-depressants or other tricyclic compounds e.g. promethazine, selective serotonin reuptake inhibitors, MAO-inhibitors and neuroleptics. The risk of seizures may also be increased in patients with epilepsy, with a history of seizures or in patients with a recognised risk for seizures e.g. drug and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone 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.

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Drug Abuse and Dependence:

Tramadol 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 have been reported. Tramadol should not be used in opioid-dependent patients. Tramadol 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 tramadol is not recommended.

Withdrawal:

Withdrawal symptoms may occur if OZTRAK 37.5/325 is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus, and unusual CNS symptoms have also been reported with abrupt discontinuation of tramadol hydrochloride. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medicine.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), eosinophilia and

systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with OZTRAK 37.5/325 must immediately be discontinued and appropriate treatment instituted.

Precautions – general:

Do not co-administer OZTRAK 37.5/325 with other tramadol or paracetamol containing medicines.

Use with alcohol:

OZTRAK 37.5/325 should not be taken with alcohol containing beverages.

Use with CNS depressants:

The administration of OZTRAK 37.5/325 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:

OZTRAK 37.5/325 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 OZTRAK 37.5/325, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medicines 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 OZTRAK 37.5/325 and appropriate treatment (e.g. fluid restriction). During OZTRAK 37.5/325 treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Excipients

Sodium

OZTRAK 37.5/325 contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use is contraindicated with:

Monoamine oxidase (MAO) Inhibitors

- Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol.

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 and other enzyme inducers

- Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.

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.

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 re-uptake 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 medicines usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

- Other opioid derivatives (including antitussive medicines and substitutive treatments).

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

- Other central nervous system depressants, such as other opioid derivatives (including antitussive medicines and substitutive treatments), other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive medicines, thalidomide and baclofen.

These medicines can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

- Sedating medicines such as benzodiazepines or related substances:
    - The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dose and duration of the concomitant use should be limited (see section 4.4).
- As medically appropriate, periodic evaluation of prothrombin time should be performed when tramadol hydrochloride/paracetamol and warfarin -like compounds are administered concurrently due to reports of increased INR.
- Post- marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.
- Concomitant administration of diflunisal and paracetamol produces a 50 % increase in paracetamol plasma levels in normal volunteers. OZTRAK 37.5/325 should be used cautiously and patients should be monitored carefully.
- Concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, quinidine and amitriptyline may inhibit the metabolism of OZTRAK 37.5/325.
- Ondansetron increased the requirement of tramadol in patients with post-operative pain.

4.6 Fertility, pregnancy and lactation

Safe use in pregnancy and lactation has not been established. OZTRAK 37.5/325 is not recommended for pregnant mothers because tramadol has been shown to cross the placenta.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility.

4.7 Effects on ability to drive and use machines

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

OZTRAK 37.5/325 can impair cognitive function and can affect a patient's ability to drive safely.

When prescribing this medicine, patients should be told that OZTRAK 37.5/325 is likely to affect your ability to drive. Patients should be told to not drive until they know how OZTRAK 37.5/325 affects them.

4.8 Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Adverse reaction	Frequency

Metabolism and nutrition disorders	Hypoglycaemia	Frequency unknown
Psychiatric disorders	Confusional state, mood altered, anxiety, nervousness, euphoric mood, sleep disorders, anorexia	Frequent
	Depression, hallucinations, depersonalisation, nightmares, delirium, drug dependence, drug abuse, impotence	Less frequent
Nervous system disorders	Dizziness, somnolence, headache, trembling	Frequent
	Involuntary muscular contractions, paraesthesia, amnesia, ataxia, convulsions, syncope, speech disorders	Less frequent
Eye disorders	Vision blurred, miosis, mydriasis	Less frequent
Ear and labyrinth disorders:	Tinnitus	Less frequent
Blood disorders	Anaemia	Less frequent
Cardiac disorders	Palpitations, tachycardia, dysrhythmia	Less frequent

Gastro-intestinal disorders:	Nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence	Frequent
	Dysphagia, melaena	Less frequent
General disorders and administration site conditions	Chills, chest pain, asthenia, fatigue, decreased weight	Less frequent
Investigations:	Transaminases increased	Less frequent
Renal and urinary disorders	Albuminuria, micturition disorders (dysuria and urinary retention), oliguria	Less frequent
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Less frequent
Skin and subcutaneous tissue disorder	Hyperhidrosis, pruritus	Frequent
	Dermal reactions (e.g. rash, urticaria).	Less frequent
Vascular disorders:	hypertension, aggravated hypertension, hot flush, hypotension	Less frequent:
Post-marketing experience		
Gastro-intestinal disorders:	Increased risk of abdominal pain, including pancreatitis	Frequency unknown

Skin and subcutaneous tissue disorders	Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE)	Frequency unknown

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 (tramadol).
- Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
- Cases of less frequent: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioedema) and anaphylaxis.
- Less frequent: Changes in appetite, motor weakness, and respiratory depression.
- Psychic side-effects may occur following administration of tramadol 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.
- Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal may occur as follows:

  Agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

  Other symptoms that have 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.
- 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 the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers 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.

4.9 Overdose:

The clinical presentation of overdosage may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both.

Tramadol

The initial symptoms of tramadol overdosage may include respiratory depression and/or seizures.

Primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all symptoms caused by overdosage, the risk of seizures is also increased with naloxone administration. Treatment of restlessness and / or convulsions is symptomatic and supportive (benzodiazepines / barbiturates).

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with OZTRAK 37.5/325 with haemodialysis or haemofiltration alone is therefore not suitable for detoxification.

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a medical practitioner immediately, or take the person to a hospital directly. 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 drugs 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.

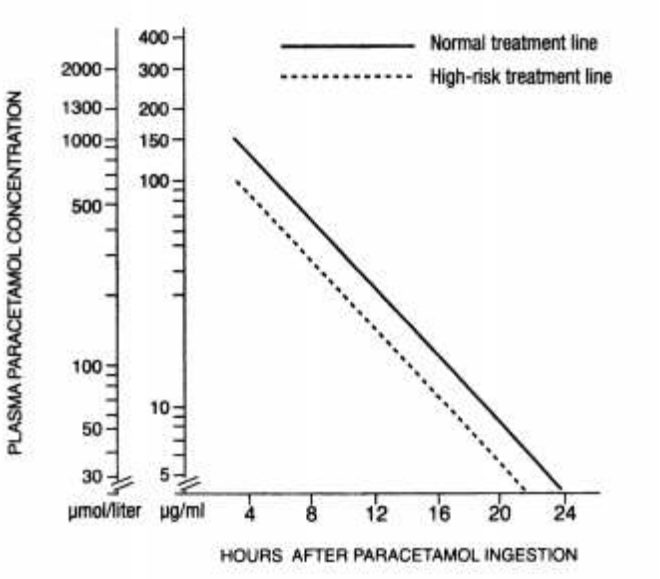
Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Treatment for paracetamol overdosage:

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 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 nomogram.



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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.2.9. Other analgesics

Opioids in combination with non-opioid analgesics, tramadol and paracetamol.

ATC Code: N02AJ13

Tramadol is a centrally acting synthetic analgesic compound whose analgesic profile can be attributed to the binding of parent and O-demethylated (M1) metabolite to μ-opioid receptors as well as the weak inhibition of neuronal re-uptake of noradrenaline and serotonin. Paracetamol also has centrally acting analgesic effects.

5.2 Pharmacokinetic properties

Absorption:

Tramadol is well absorbed after oral administration, reaching peak activity in 2 to 3 hours. The mean absolute bioavailability of a single 100 mg oral dose is approximately 75 %, increasing to approximately 90 % with multiple dosing. Oral absorption of paracetamol following administration of OZTRAK 37.5/325 gives a peak plasma concentration of paracetamol within one hour and is not affected by co-administration with tramadol.

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.

Metabolism:

Tramadol and paracetamol are both extensively metabolised in the liver.

Elimination:

Approximately 30 % of tramadol is excreted unchanged in the urine. Tramadol and its metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of tramadol and its M1 metabolite are approximately 6 and 7 hours respectively. Paracetamol is eliminated from the body primarily by formation of glucuronide and sulphate conjugates in a dose-dependent manner. The half-life of paracetamol is about 2 - 3 hours in adults. Less than 9 % of paracetamol is excreted unchanged in the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, maize starch, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate, Opadry yellow coating containing hypromellose, iron oxide yellow, titanium dioxide and triacetin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

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.

6.5 Nature and contents of container

OZTRAK 37.5/325 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.

Pack sizes: 30 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenburg Roads

Victory Park

Johannesburg

2195

8 REGISTRATION NUMBER(S):

47/2.9/1054

9 DATE OF FIRST AUTHORISATION

18 May 2022

10 DATE OF REVISION OF THE TEXT

16 August 2023

Initial: 16/08/2023