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SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

TAMOLTRA (37,5 mg/325 mg) film coated tablet

TAMOLTRA FORTE (75 mg/650 mg) film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

TAMOLTRA FORTE: Each film coated tablet contains tramadol hydrochloride 75 mg and paracetamol 650 mg.

Sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

TAMOLTRA: Slightly yellow-brown, oval, convex film coated tablets.

TAMOLTRA FORTE: Slightly orange, oval, biconvex film coated tablets widely scored on both sides.

4. CLINICAL PARTICULARS

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4.1 Therapeutic indications

TAMOLTRA and TAMOLTRA FORTE are indicated for the management of moderate to moderately severe pain in adults.

TAMOLTRA and TAMOLTRA FORTE are not recommended for minor pain that may be treated adequately through lesser means.

4.2 Posology and method of administration

Posology

TAMOLTRA: To be used in adults and children over 16 years of age.

TAMOLTRA FORTE: To be used in adults.

DO NOT EXCEED THE RECOMMENDED DOSE.

TAMOLTRA: Adults and children over the age of 16

For the management of pain, the recommended dose of TAMOLTRA is 1 or 2 tablets every 4 to 6 hours, as needed for pain relief, up to a maximum of 8 tablets per day.

TAMOLTRA FORTE: Adults

The recommended dose of TAMOLTRA FORTE is 1 tablet every 4 to 6 hours as needed.

The maximum total dose per day is 4 tablets.

As with all analgesic medicines, a titration period of several days with gradual dose increases at the initiation of TAMOLTRA and TAMOLTRA FORTE therapy may be beneficial for some patients.

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Clinical studies with tramadol in patients with moderate to moderately severe chronic pain indicated that the tolerability of tramadol can be improved by starting at a lower dose with gradual upward titration to reach doses that provide sufficient pain relief.

Special populations

Elderly population (65 years of age and older)

No overall differences, about safety or pharmacokinetics, were noted between subjects ≥ 65 years of age and younger subjects.

Renal insufficiency / dialysis

In patients with renal insufficiency, the elimination of tramadol is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patients' requirements.

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

Hepatic impairment

TAMOLTRA and TAMOLTRA FORTE should not be used in patients with moderate to severe liver impairment (see section 4.3).

Paediatric population

TAMOLTRA: Not indicated for use in children under the age of 16 years, as safety and efficacy have not been established.

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TAMOLTRA FORTE: Not recommended in patients under 18 years old.

Method of administration

For oral use

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

Tablets can be administered without regard to food.

Missed dose:

Doctors should advise patients who forget to take TAMOLTRA or TAMOLTRA FORTE to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- TAMOLTRA and TAMOLTRA FORTE are contraindicated in patients with a known hypersensitivity to tramadol, paracetamol, or other opioids such as codeine any of the other ingredients mentioned in section 6.1.
- TAMOLTRA and TAMOLTRA FORTE are also contraindicated in cases of moderate to severe liver function impairment and in acute intoxication with alcohol
- TAMOLTRA and TAMOLTRA FORTE are contraindicated in combination with hypnotic substances or centrally acting analgesics, opioids, or psychotropic medicines
- TAMOLTRA and TAMOLTRA FORTE should not be administered to patients receiving

monoamine oxidase inhibitors (MAOIs) or within two weeks of their withdrawal

- TAMOLTRA and TAMOLTRA FORTE must not be used for the narcotic withdrawal treatment
- TAMOLTRA and TAMOLTRA FORTE should not be administered to patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions
- TAMOLTRA and TAMOLTRA FORTE should not be given to patients with increased intracranial pressure or central nervous system depression due to head injury or cerebral disease
- TAMOLTRA and TAMOLTRA FORTE can cause seizures (convulsions), hence it should not be used in patients with epilepsy or seizures of any cause (see section 4.4).

4.4 Special warnings and precautions for use

TAMOLTRA and TAMOLTRA FORTE contain 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.

- dosages in excess of those recommended may cause severe liver damage. Patients suffering from liver or kidney disease should only take paracetamol containing products under medical supervision.
- TAMOLTRA and TAMOLTRA FORTE should not be used concurrently with any other medicines containing tramadol or paracetamol

- TAMOLTRA and TAMOLTRA FORTE are not recommended in severe renal insufficiency (creatinine clearance <10 mL/mm).
- TAMOLTRA and TAMOLTRA FORTE 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.
- TAMOLTRA and TAMOLTRA FORTE is not recommended for use in patients with severe respiratory insufficiency
- TAMOLTRA and TAMOLTRA FORTE are not suitable as a substitute for opioid dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms
- concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5)
- caution should be exercised in using TAMOLTRA and TAMOLTRA FORTE in patients with impaired renal function and patients who are in shock. In patients with cranial trauma, biliary tract disorders, events of reduced consciousness for unknown reasons, respiratory disorders and patients suffering from emotional disturbances or depression or using alcohol in excess, or with an increased intracranial pressure, TAMOLTRA and TAMOLTRA FORTE should be taken with extreme caution.

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 re-uptake inhibitors, MAO-inhibitors, and neuroleptics (see section 4.3). 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 (see section 4.3). Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with tramadol.

Anaphylactic reactions

Patients with a history of anaphylactic reactions to codeine and other opioids may be at increased risk and should therefore not receive TAMOLTRA or TAMOLTRA FORTE.
Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol.
Patients should be advised to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

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 for signs of tramadol overdose, such as respiratory depression, is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Even at labelled dosage regimens, individuals who are ultra-rapid metabolisers may have life-threatening or fatal respiratory depression or experience signs of toxicity such as extreme sleepiness, confusion, shallow breathing, small pupils, nausea, vomiting, constipation, and lack of appetite (see section 4.9).

Population	**Prevalence**
African/Ethiopian	29 %
African American	3.4 % to 6.5 %
Asian	1.2 % to 2 %
Caucasian	3.6 % to 6.5 %
Greek	6.0 %
Hungarian	1.9 %
Northern European	1 % to 2 %

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 patients who are chronically using opioids, treatment with tramadol is not recommended.

There is an increased risk of addiction in patients with a personal or family history of substance abuse or mental health disorders.

TAMOLTRA and TAMOLTRA FORTE should not be given to patients who are suicidal or prone to addiction.

Withdrawal

Withdrawal symptoms may occur if TAMOLTRA and TAMOLTRA FORTE 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.

Gradual tapering, using TAMOLTRA and TAMOLTRA FORTE, is preferred wherever possible, although in some cases it may be necessary to change to a different opioid because of ease of use, duration of action and ability to taper the dose. Clonidine may help to suppress some of the symptoms of abrupt opioid withdrawal, such as anxiety, insomnia, and muscle ache.

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 SCARs,
treatment with TAMOLTRA and TAMOLTRA FORTE must immediately be discontinued, and appropriate treatment instituted.

Hyponatraemia:

Hyponatraemia has been reported with the use of TAMOLTRA and TAMOLTRA FORTE, 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 TAMOLTRA and TAMOLTRA FORTE and appropriate treatment (e.g., fluid restriction). During treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Use with general anaesthetics

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, as in TAMOLTRA and TAMOLTRA FORTE, during light planes of anaesthesia should be avoided.

Use with CNS depressants:

The administration of TAMOLTRA and TAMOLTRA FORTE concurrently with central nervous system (CNS) depressants, such as alcohol, opioids, anaesthetic medicines, phenothiazines,

tranquilisers or sedative hypnotics, is likely to intensify and prolong CNS effects including profound sedation and respiratory depression.

TAMOLTRA and TAMOLTRA FORTE should be used with caution and in reduced dosages when administered to patients receiving CNS depressants (see section 4.5).

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol, as in TAMOLTRA and TAMOLTRA FORTE, in combination with other serotonergic medicines or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic medicines is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic

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 or stopping the total opioid dosage.

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Precautions – general

Do not co-administer TAMOLTRA and TAMOLTRA FORTE with other tramadol or paracetamol containing products.

Use with alcohol

TAMOLTRA and TAMOLTRA FORTE should not be taken with alcohol containing beverages.

Use in renal disease

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

Paediatric population

TAMOLTRA and TAMOLTRA FORTE are not indicated for use in children and adolescents under the age of 16 (see sections 4.1 and 4.2).

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 and noradrenergic effects (see section 4.8).

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

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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 medicinal products 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 4.2), tricyclic antidepressants and mirtazapine may cause serotonin toxicity.
- serotonin syndrome is likely when one of the following is observed:
    - spontaneous clonus

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- 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.
- concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, quinidine, and amitriptyline may inhibit the metabolism of tramadol.

Changes of tramadol in serum concentration have been seen with concomitant administration with cimetidine. Therefore, patients receiving chronic therapy with cimetidine should not alter the dosage regimen of TAMOLTRA and TAMOLTRA FORTE treatment

- 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. TAMOLTRA and TAMOLTRA FORTE should be used cautiously, and patients should be monitored carefully. The absorption of paracetamol may be enhanced by metoclopramide and reduced by cholestyramine
- 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.

Pregnancy

TAMOLTRA and TAMOLTRA FORTE is not recommended for pregnant mothers because tramadol has been shown to cross the placenta.

Data regarding paracetamol:

Epidemiological studies in human pregnancy have shown no teratogenic 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 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

TAMOLTRA and TAMOLTRA FORTE should not be used during breast feeding.

Data regarding paracetamol:

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding 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 breast-fed infants of 3 % of the maternal weight-adjusted dosage. For this reason, tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

Fertility

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

4.7 Effects on ability to drive and use machines

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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.

TAMOLTRA and TAMOLTRA FORTE can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told that TAMOLTRA and TAMOLRA FORTE is likely to affect your ability to drive. Patients should be told to not drive until they know how TAMOLTRA and TAMOLTRA FORTE affects them.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequently reported undesirable effects of the paracetamol /tramadol combination in clinical trials were gastrointestinal and central nervous system effects. Nausea, dizziness, and somnolence were observed in more than 10 % of patients.

b) Tabulated summary of adverse reactions

Side effects for TAMOLTRA AND TAMOLTRA FORTE

Tramadol and Paracetamol:

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Anaemia
Immune system disorders	Frequency unknown	Fixed eruption*

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Metabolism and nutrition disorders	Frequency unknown	Hypoglycaemia, hyponatraemia*/syndrome of inappropriate antidiuretic hormone*
Psychiatric disorders	Frequent Less frequent	Confusional state, mood altered, anxiety, nervousness, euphoric mood), sleep disorders, anorexia, insomnia, nervousness Depression, hallucinations, depersonalisation, nightmares, delirium, drug dependence, drug abuse, impotence, amnesia, emotional liability, unusual thought processes, suicidal tendency
Nervous system disorders	Frequent Less frequent	Dizziness, somnolence, headache, trembling Involuntary muscular contractions, paraesthesia, ataxia, convulsions, syncope, speech disorders, hypertonia, migraine, aggravated migraine, stupor, vertigo
Eye disorders	Less frequent	Vision blurred, miosis, mydriasis, abnormal vision
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Palpitations, tachycardia, dysrhythmia
Vascular disorders	Less frequent	Hypertension, aggravated hypertension, hot flushes, hypotension, orthostatic hypotension

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Respiratory, thoracic, and mediastinal disorders	Less frequent	Dyspnoea
Gastrointestinal disorders	Frequent Less frequent	Nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence Dysphagia, melaena, tongue oedema
Hepatobiliary disorders	Less frequent	Liver test abnormalities, hepatitis
Skin and subcutaneous tissue disorders	Frequent Less frequent	Hyperhidrosis, pruritus Dermal reactions (e.g., rash, urticaria)
Renal and urinary disorders	Less frequent	Albuminuria, micturition disorders (dysuria and urinary retention), oliguria, renal colic, renal failure, sterile pyuria
General disorders and administrative site conditions	Less frequent	Chills, chest pain, asthenia, fatigue, decreased weight, withdrawal syndrome
Investigations	Less frequent	Transaminases increased, hypothrombinaemia, elevated creatinine

*Post marketing

Tramadol:

System Organ Class	**Frequency**	**Side effects**

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Blood and lymphatic system disorders	Frequency unknown	Elevated creatinine and rare alterations of warfarin effect, including elevation of prothrombin times*, hyponatraemia*
Immune system disorders	Less frequent	Allergic reactions with respiratory symptoms (e.g., dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
Metabolism and nutrition disorders	Less frequent Frequency unknown	Changes in appetite, motor weakness, weight loss Hypoglycaemia*
Psychiatric disorders	Less frequent	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)
Nervous system disorders	Frequency unknown	Cognitive dysfunction, Serotonin syndrome
Cardiac disorders	Less frequent	Bradycardia
Vascular disorders	Less frequent	Postural hypotension, collapse
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Respiratory depression Worsening of asthma has been reported though a causal relationship has not been established, hiccups

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Gastrointestinal disorders	Less frequent	Increased risk of abdominal pain, including pancreatitis*
Hepatobiliary disorders	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	Frequency unknown	Stevens Johnson Syndrome* /TENS*
General disorders and administrative site conditions	Frequency unknown	Drug withdrawal syndrome (with symptoms including agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor, gastrointestinal symptoms, panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus, and unusual CNS symptoms)

*Post marketing

Paracetamol

1. hypersensitivity, including skin rash, may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis
2. 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
3. cases of serious skin reactions have been reported.

   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.

*Post marketing

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 professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

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.

Paracetamol

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 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.

Management of overdose:

Tramadol

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 TAMOLTRA and TAMOLTRA FORTE 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.

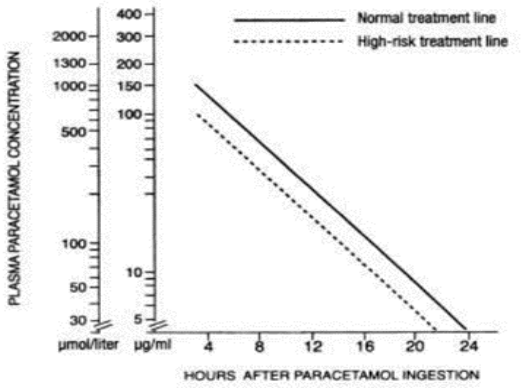
Treatment for paracetamol overdosage

Although evidence is limited it is recommended that any adult person who have ingested 5 – 10 g or more of paracetamol (or child who has had more than 140 mg/kg) within the preceding 4 hours should have the stomach emptied by gastric 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 requires treatment in patients susceptible to paracetamol poisoning. In patients who are stuperose or comatose, endotracheal tubing should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of overdosage, 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 overdose 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. Further treatment is symptomatic and supportive.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics; tramadol and paracetamol

ATC code: N02AJ13

Pharmacological classification: A.2.9. Other Analgesics

Mechanism of action

Tramadol is a centrally acting synthetic analgesic compound whose analgesic profile can be attributed to the binding of parent compound 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.

The tramadol hydrochloride/paracetamol combination is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the healthcare provider or doctor.

5.2 Pharmacokinetic properties

Absorption:

After oral administration tramadol is well absorbed, and peak activity is reached within 2 to 3 hours. Bioavailability can increase to up to 90 % with multiple dosing. Peak plasma concentration of paracetamol after oral administration is within 1 hour. The absorption of paracetamol is not affected by the co-administration of tramadol.

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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 mealtimes.

Distribution:

Tramadol has a high tissue affinity (Vd, β=203 ± 40 L). It has a plasma protein binding is 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 relatively small portion (~20 %) of paracetamol is bound to plasma proteins.

Biotransformation:

Tramadol and paracetamol are both extensively metabolised in the liver.
Tramadol undergoes extensive hepatic metabolism by a number of pathways including CYP2D6 and CYP3A4, as well as conjugation (see section 4.5).

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. Plasma elimination half-lives of tramadol and the O-demethylated metabolite are about 6 and 7 hours respectively. The metabolite M1 has analgesic properties and is more potent than the parent medicine. 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.

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Paracetamol is principally metabolised by 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 metabolized by cytochrome P 450 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:

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. 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.
In renal insufficiency, the half-life of both compounds is prolonged.

6. PHARMACEUTICAL PARTICULARS

APPROVED PROFESSIONAL INFORMATION

6.1 List of excipients

Tablet core

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Sodium starch glycolate (Type A)

TAMOLTRA Film coating

Opadry Yellow 15B82958 composition:

Hypromellose

Polyethylene glycol 400

Polysorbate 80

Titanium dioxide (C.I. 77891)

Yellow iron oxide (C.I. 77492)

TAMOLTRA FORTE Film coating

Red iron oxide, E172

Opadry Yellow 15B82958 composition:

Hypromellose

Macrogol 400 (polyethylene glycol)

Polysorbate 80

Titanium dioxide

Yellow iron oxide

6.2 Incompatibilities

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APPROVED PROFESSIONAL INFORMATION

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

TAMOLTRA: Store at or below 30 °C in a cool, dry place.

TAMOLTRA FORTE: Store at or below 25 °C in a cool, dry place.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

TAMOLTRA is available in blister packs consisting of PVC/PVDC, white film and aluminium foil, with 20, 30 or 60 tablets packed in an outer carton.

TAMOLTRA FORTE is available in blister packs consisting of PVC/PVDC, white film and aluminium foil, with 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 tablets packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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8. REGISTRATION NUMBER(S)

TAMOLTRA: A46/2.9/0976

TAMOLTRA FORTE: A47/2.9/0926

9. DATE OF FIRST AUTHORISATION

TAMOLTRA: 27 July 2017

TAMOLTRA FORTE: 03 May 2022.

10. DATE OF REVISION OF THE TEXT

TAMOLTRA: 27 February 2025

TAMOLTRA FORTE: 27 February 2025