Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol.

Excipients with known effect:
Each film-coated tablet contains 2.651 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
An oblong, light yellow film-coated tablet debossed with “P/T” on one side and “M” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tramadol hydrochloride/Paracetamol is indicated for the symptomatic treatment of moderate to severe pain.
The use of Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see section 5.1).

4.2 Posology and method of administration

Posology
The use of Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol.

The dose should be adjusted to intensity of pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.

The total dose of 8 tablets (equivalent to 300 mg of tramadol and 2600 mg of paracetamol) per day should not be exceeded. The dosing interval should not be less than 6 hours.

Adults and adolescents (12 years and older)
An initial dose of two tablets of Tramadol hydrochloride/Paracetamol (equivalent to 75 mg of tramadol and 650 mg of paracetamol) is recommended. Additional dose can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg of tramadol and 2600 mg of paracetamol) per day. The dosing interval should not be less than 6 hours.

Tramadol hydrochloride/Paracetamol should under no circumstances be taken for longer than is strictly necessary (see section 4.4). If repeated use or long term treatment with Tramadol hydrochloride/Paracetamol is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (whenever possible, with breaks in treatment) to assess whether the treatment needs to be continued.

Geriatric Patients
A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

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 patient's requirements.

The use of Tramadol hydrochloride/Paracetamol in patients with severe renal insufficiency (creatinine clearance < 10 ml/min) is not recommended.

Hepatic impairment
In patients with hepatic impairment the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements (see section 4.4). Because of the presence of paracetamol, Tramadol hydrochloride/Paracetamol should not be used in patients with severe hepatic impairment (see section 4.3).

Paediatric population
The safety and efficacy of tramadol/paracetamol in children under 12 years of age has not been established. Therefore, treatment in this patient population is not recommended.

Method of administration
Oral use.
Tablets must be swallowed whole, with a sufficient quantity of liquid. They should not be broken or chewed.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Acute alcohol intoxication, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs.
- Concomitant treatment with monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal (see section 4.5).
- Severe hepatic impairment.
- Epilepsy not controlled by treatment (see section 4.4).

4.4 Special warnings and precautions for use

Warnings:

- Serotonin syndrome:Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9). If concomitant treatment with other serotonergic agents 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 drugs usually brings about a rapid improvement.

- In adults and adolescents aged 12 years and older, the maximum daily dose of 8 tablets of tramadol/paracetamol should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to concurrently take any other medicines containing paracetamol (including over-the-counter medicines) or tramadol, without the advice of a physician.

- Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

- In severe renal insufficiency (creatinine clearance < 10 ml/min), tramadol/paracetamol is not recommended.

- In patients with severe hepatic impairment, tramadol/paracetamol should not be used (see section 4.3). The hazards of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. In cases of moderate hepatic insufficiency, extending the dosage interval should be carefully considered.

- Tramadol/paracetamol is not recommended in cases of severe respiratory insufficiency.

- Tramadol is not suitable as a substitute therapy in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

- Convulsions have been reported in patients susceptible to seizures receiving treatment with tramadol and/or taking other medications that lower the seizure threshold, in particular selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthetics. Epileptic patients controlled by a treatment, or those susceptible to seizures should only be treated with tramadol/paracetamol if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended doses. The risk may be increased when the doses of tramadol exceed the recommended upper dose limit.

- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5).

- Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Tramadol hydrochloride/Paracetamol tablets and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol hydrochloride/Paracetamol tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

- Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleeprelated 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.

- Adrenal insufficiency
Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

- *CYP2D6 metabolism*
Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.
General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

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%

- Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

- Children with compromised respiratory function
Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

Precautions:
- Tolerance and physical and/or psychological dependence may develop, especially after long-term use, even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly (see section 4.2). In opioid-dependent patients and patients with a history of drug abuse or dependence, treatment should only be for short periods and under medical supervision. Tramadol/paracetamol should be used with caution in patients with cranial trauma, patients prone to convulsions, patients with biliary tract disorders, patients in a state of shock, patients in an altered state of consciousness for unknown reasons, patients with problems affecting the respiratory centre or respiratory function or those with raised intracranial pressure.

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

- In some patients, paracetamol overdose may cause liver toxicity.

- Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur even at therapeutic doses and for short term treatment (see section 4.8). Withdrawal symptoms may be avoided by tapering the dose at the time of discontinuation especially after longer treatment periods. Rarely, cases of dependence and abuse have been reported (see section 4.8).

- In one study the use of tramadol with enflurane and nitrous oxide during general anaesthesia was reported to enhance intra-operative recall. Until further information becomes available, use of tramadol during light planes of anaesthesia should be avoided.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant use is contraindicated with:

- Non-selective MAO inhibitorsRisk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state and even coma.
- Selective MAO-A inhibitorsBy extrapolation from non-selective MAO inhibitors.Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state and even coma.
- Selective MAO-B inhibitorsSymptoms of central excitation similar to those of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state and even coma.

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

Concomitant use is not recommended with:

- AlcoholAlcohol increases the sedative effect of opioid analgesics.The effect on alertness may make driving vehicles and using machines dangerous.Consumption of alcoholic drinks and medicinal products containing alcohol should be avoided.
- Carbamazepine and other enzyme inducersRisk of reduced efficacy and shorter duration due to reduced plasma concentrations of tramadol.
- Opioid agonists/antagonists (buprenorphine, nalbuphine, pentazocine)Decrease in 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 other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

- Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), triptans, MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4)

- 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, such as other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates (e.g. phenobarbital), other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics (antipsychotics), centrally-acting antihypertensive drugs, thalidomide and baclofen.

These medicines can cause worsening of central depression. The effect on alertness may make driving vehicles and using machines dangerous.

- Sedative medicines such as benzodiazepines or related drugs:The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).
- As medically appropriate, periodic evaluation of prothrombin time should be performed when tramadol/paracetamol and warfarin like compounds (vitamin K antagonists) are administered concurrently due to reports of increased INR.Other medicines known to inhibit CYP3A4, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol (N-demethylation) and, probably, also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.
- The speed of absorption of paracetamol may be increased by metoclopramide or domperidone. Absorption may be reduced by cholestyramine.
- In a limited number of studies, the pre- or post-operative use of the antiemetic 5-HT_3 antagonist, ondansetron, increased the requirement for tramadol in patients with post-operative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy
As tramadol/paracetamol is a fixed combination of active substances that includes tramadol, it should not be used during pregnancy.

Data regarding paracetamol:

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

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 cause changes in the respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to withdrawal symptoms in the neonate, after birth, as a consequence of habituation.

Breast-feeding
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.

Data regarding paracetamol:

Paracetamol is excreted in breast milk but not in clinically significant quantities. Available published data do not contraindicate breast-feeding by women who are taking medicines containing paracetamol alone.

Data regarding tramadol:

Tramadol and its metabolites are found in small quantities in human breast milk. An infant could ingest approximately 0.1% of the dose taken by the mother. Tramadol should not be taken during breast-feeding.

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

Animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of tramadol and paracetamol.

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 use machines.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

The most commonly reported undesirable effects in clinical studies conducted with the tramadol/paracetamol combination were nausea, dizziness and somnolence, which were observed in more than 10% of patients.

The following terms have been used to classify the incidence of undesirable effects:
Very common (≥ 1/10)
Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Metabolism and nutrition disorders	
Not known:	Hypoglycaemia.
Psychiatric disorders	
Common:	Confusional state, mood altered (anxiety, nervousness, euphoric mood), sleep disorders.
Uncommon:	Depression, hallucinations, nightmares.
Rare:	Delirium, drug dependence.
Nervous system disorders	
Very common:	Dizziness, somnolence.
Common:	Headache, trembling.
Uncommon:	Involuntary muscular contractions, paraesthesia, amnesia.
Rare:	Ataxia, convulsions, syncope, speech disorders.
Not known:	Serotonin syndrome.
Eye disorders	
Rare:	Vision blurred, miosis, mydriasis.
Ear and labyrinth disorders	
Uncommon:	Tinnitus.
Cardiac disorders	
Uncommon:	Palpitations, tachycardia, arrhythmia.
Vascular disorders	
Uncommon:	Hypertension, hot flush.
Respiratory thoracic and mediastinal disorders	
Uncommon:	Dyspnoea.
Gastrointestinal disorders	
Very common:	Nausea.
Common:	Vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence.
Uncommon:	Dysphagia, melaena.
Skin and subcutaneous tissue disorders	
Common:	Hyperhidrosis, pruritus.
Uncommon:	Dermal reactions (e.g. rash, urticaria).
Renal and urinary disorders	
Uncommon:	Albuminuria, micturition disorders (dysuria, urinary retention).
General disorders and administration site conditions	
Uncommon:	Chills, chest pain.
Investigations	
Uncommon:	Transaminases increased.
Post-marketing surveillance	
Psychiatric disorders	
Very rare:	Abuse.

The following undesirable effects have not been observed in clinical studies, but are known to be related to the administration of tramadol or paracetamol:
Tramadol

Blood and lymphatic system disorders	
Not known:	The post-marketing surveillance of tramadol has revealed rare cases of alterations in the effect of warfarin, including prothrombin time prolongation.
Immune system disorders	
Rare:	Allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis reaction.
Metabolism and nutrition disorders	
Rare:	Changes in appetite.
Psychiatric disorders	
Very rare:	The following symptoms have been observed following the sudden withdrawal of tramadol: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual central nervous system symptoms.
Not known:	Other withdrawal symptoms, similar to those occurring with opiate withdrawal, may occur: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Psychic side effects may occur after the administration of tramadol, with individual variations in intensity and nature (depending on personality and treatment duration). These may include: mood changes (usually euphoric mood, occasionally dysphoria), changes in activity (usually suppression, occasionally increase), and changes in the cognitive and sensorial capacity (e.g. decision behaviour, perception disorders).
Cardiac disorders	
Not known:	Postural hypotension, bradycardia, collapse.
Respiratory, thoracic and mediastinal disorders	
Rare:	Respiratory depression.
Not known:	Exacerbation of asthma has been reported, but a causal relationship with the medicine has not been established. Hiccups.
Musculoskeletal and connective tissue disorders	
Rare:	Motor weakness.

Paracetamol

Blood and lymphatic system disorders	
Not known:	There have been reports of blood dyscrasias, including thrombocytopenia and agranulocytosis, but these were not necessarily causally associated with paracetamol. Several reports have suggested that paracetamol may cause hypoprothrombinaemia when administered with warfarin like compounds. In other studies there were no changes in prothrombin time.
Immune system disorders	
Rare:	Hypersensitivity may occur, including skin rash.
Skin and subcutaneous tissue disorders	
Very rare:	Very rare cases of serious skin reactions have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
HPRA Pharmacovigilance,
Website: www.hpra.ie.

4.9 Overdose

Tramadol/paracetamol is a fixed combination of active substances. In case of overdose, symptoms may include the signs and symptoms of tramadol or paracetamol toxicity or of toxicity of both active substances.

Serotonin syndrome has also been reported.

Symptoms of tramadol overdose
In principle, 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 including coma, convulsions and respiratory depression which can cause respiratory arrest.

Symptoms of paracetamol overdose:
An overdose is of particular concern in young children. Symptoms of paracetamol overdose 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 in glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with tubular necrosis may develop, even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have also been reported.

Liver damage is possible in adults who have taken 7.5 g to 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 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 the overdose, to measure plasma concentrations of paracetamol and tramadol and in order to perform hepatic tests;
- Hepatic tests should be performed at the start (of overdose) and repeated every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalises after one or two weeks;
- The stomach should be emptied by inducing vomiting by irritation (when the patient is conscious) or gastric lavage;
- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be initiated; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam;
- Tramadol is minimally eliminated from the blood by haemodialysis or haemofiltration. Therefore treatment of acute intoxication by tramadol/paracetamol with haemodialysis or haemofiltration alone is not suitable for detoxification.

Immediate treatment of paracetamol overdose is essential. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. If any adult or adolescent has ingested around 7.5 g or more of paracetamol in the preceding 4 hours, or any child has ingested ≥150 mg/kg of paracetamol in the preceding 4 hours, gastric lavage should be performed. Paracetamol concentrations in blood should be measured at 4 hours or later after ingestion in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or intravenous N-acetylcysteine (NAC), which may have a beneficial effect up to at least the 48 hours after overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be administered if the time from overdose is over 8 hours, and continued for a full course of treatment. Treatment with NAC should be started immediately when massive overdose is suspected. General supportive measures must be available.

Regardless of the reported quantity of paracetamol ingested, the antidote for paracetamol, NAC, should be given as quickly as possible, either orally or intravenously, if possible within 8 hours of the overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, other opioids; tramadol, combinations, ATC code: N02AX52.

Mechanism of action
Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure, non-selective agonist of the μ, δ and κ opioid receptors, with a higher affinity for the μ receptors. Other mechanisms that 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, gastrointestinal motility is not affected. The cardiovascular effects are usually mild. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.
The exact 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 as indicated by the physician.

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 dose of tramadol/paracetamol (37.5 mg + 325 mg), peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 µg/ml (paracetamol), are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol). The mean elimination half-lives $t_{1/2}$ are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2.5 h (paracetamol).

During pharmacokinetic studies in healthy volunteers, after single and repeated oral administration of tramadol/paracetamol, no clinically significant changes were observed in the kinetic parameters obtained for each of the active ingredients compared with the parameters of the active ingredients when used alone.

Absorption
Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single dose of 100 mg 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 almost complete, and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in 1 hour and are not modified by concomitant administration of tramadol.

The oral administration of tramadol/paracetamol with food has no significant effect on peak plasma concentrations or extent of absorption of either tramadol or paracetamol; consequently, tramadol/paracetamol may be administered independently of meal times.

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

Paracetamol appears to be widely distributed throughout most body tissue except fat. Its apparent volume of distribution is around 0.9 l/kg. A relatively small portion (~20%) of paracetamol binds to plasma proteins.

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

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Tramadol is metabolised by 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 by 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. Plasma concentrations of M1 are several-fold lower than those of tramadol and it is unlikely that the contribution to the clinical effect will change with multiple dosing.

Paracetamol is principally metabolised in the liver through two major hepatic routes: glucuronidation and sulfation. 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 compound (N-acetyl-benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in the urine after conjugation with cysteine and mercapturic acid.

However, during massive overdose, the quantity of this metabolite is increased.

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

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

No preclinical study has been performed with the fixed combination (tramadol and paracetamol) to evaluate its carcinogenic and mutagenic effects or its effects on fertility.

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

The tramadol/paracetamol combination has been shown to be embryotoxic and foetotoxic in the rat at maternotoxic doses (50/434 mg/kg tramadol/paracetamol), i.e. 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus result in decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe maternotoxic effects (10/87 and 25/217 mg/kg tramadol/paracetamol) had no toxic effects on the embryo or the foetus.

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

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

Animal studies at very high doses of tramadol showed effects on organ development, ossification and neonatal mortality associated with maternotoxicity. The reproductive fertility and development of offspring were not affected. 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 doses of paracetamol.

Animal studies and extensive human experience to date have shown no evidence of reproductive toxicity

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Maize starch, pregelatinised
Povidone (K29/32)
Crospovidone
Stearic acid
Silica, colloidal anhydrous
Magnesium stearate

Film-coating:
Hypromellose 6cP
Lactose monohydrate
Titanium dioxide (E171)
Macrogol 300

Triacetin
Iron oxide yellow (E172)
Macrogol 4000
Hypromellose 15cP
Hypromellose 3cP
Hypromellose 50cP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
Bottles: Use within 100 days of opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

HDPE bottles with polypropylene (PP) child-resistant closures with induction sealing liner containing 100 film-coated tablets.

HDPE bottles with polypropylene (PP) screw cap closures with induction sealing liner containing 500 film-coated tablets (dispensing pack).

The HDPE bottle pack may either be placed in an outer cardboard carton or provided without a carton based on market requirement.

Clear/transparent PVC-PVdC/Aluminium foil blisters in cardboard cartons containing 2, 5, 10, 20, 30, 40, 50, 60, 90, 100, 200 film-coated tablets.

Clear/transparent PVC-PVdC/Aluminium foil perforated unit dose blisters in cardboard cartons containing 20 x 1 and 60 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd., T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/221/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 7th March 2014

Date of Last Renewal: 18th June 2018

10 DATE OF REVISION OF THE TEXT

June 2022