Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Yellowish, cylindrical, biconvex, film-coated tablet of 11mm diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tramadol/Paracetamol Rowa tablets are indicated for the symptomatic treatment of moderate to severe pain.

The use of Tramadol/Paracetamol Rowa should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see also Section 5.1).

4.2 Posology and method of administration

Posology

Adults and adolescents (12 years and older):
The use of Tramadol/Paracetamol Rowa 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 the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.
An initial dose of two tablets of Tramadol/Paracetamol Rowa is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.
The dosing interval should not be less than six hours.

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

Paediatric population
The effective and safe use of Tramadol/Paracetamol Rowa has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

Elderly 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 and hepatic impairment:
In patients with renal and/or hepatic 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.

Hepatic impairment:
In patients with severe hepatic impairment Tramadol/Paracetamol Rowa should not be used (see Section 4.3). In moderate cases prolongation of the dosage interval should be carefully considered (see Section 4.4).

Method of administration:

Oral use
Tablets must be swallowed whole, with a sufficient quantity of liquid.

Treatment goals and discontinuation
Before initiating treatment with Tramadol/Paracetamol Rowa a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

4.3 Contraindications

- Hypersensitivity to tramadol, paracetamol or to any of the excipients (listed in section 6.1)
- Acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids orpsychotropic drugs
- Tramadol/Paracetamol Rowa should not be administered to patients who are receiving monoamine oxidase 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:

· **In adults and adolescents 12 years andolder:**

The maximum dose of 8 tablets of Tramadol/Paracetamol Rowa 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 physician.

· **Renalimpairment:**

In severe renal insufficiency (creatinine clearance <10 ml/mm), Tramadol/Paracetamol Rowa is not recommended.

· **Hepaticimpairment:**

In patients with severe hepatic impairment Tramadol/Paracetamol Rowa should not be used (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.

· **Respiratoryimpairment:**

In severe respiratory insufficiency, Tramadol/Paracetamol Rowa is not recommended.

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

- Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Tramadol/Paracetamol Rowa only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended dose

levels. The risk may be increased when 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).

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.

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.

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.

Precautions

<u>Tolerance and opioid use disorder (abuse and dependence)</u>
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Tramadol/Paracetamol Rowa. Repeated use of Tramadol/Paracetamol Rowa can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of |product name] may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Tramadol/Paracetamol Rowa and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs

occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Tramadol/Paracetamol Rowa should be used with caution in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory centre or the respiratory function, or with an increased intracranial pressure.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin . If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring, is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Paracetamol in over-dosage may cause hepatic toxicity in some patients.

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

Symptoms of withdrawal reaction, 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 it at the time of discontinuation especially after long treatment periods. Rarely, cases of dependence and abuse have been reported (see section 4.8).

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of tramadol 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/Paracetamol Rowa 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).

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.

Tramadol/Paracetamol Rowa contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use is contraindicated with:

- **Non-selective MAOInhibitors**

Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

· **Selective-A MAOInhibitors**

Extrapolation from non-selective MAO inhibitors
Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, **confusion, even coma.**

· **Selective-B MAOInhibitors**

Central excitation symptoms evocative of a serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, 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 medicinal products containing alcohol.

- **Carbamazepine and other enzymeinducers** 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 other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.
- *Sedative medicines such as benzodiazepines or relateddrugs:*

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).

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

- 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, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen. These drugs can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
- The concomitant use of Tramadol/Paracetamol Rowa with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

- Other medicinal products known to inhibit CYP3A4, such as ketoconazole and erythromycin, might 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.

- As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol/Paracetamol Rowa and warfarin like compounds are administered concurrently due to reports of increased INR.
- In a limited number of studies, the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

- 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)

4.6 Fertility, pregnancy and lactation

Pregnancy:
Since Tramadol/Paracetamol Rowa is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

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

Data regarding paracetamol:
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.

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.

Since Tramadol/Paracetamol Rowa is a fixed combination of active ingredients including tramadol, it should not be ingested during breast-feeding.

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**.**

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 medicinal products containing only paracetamol.

Fertility:
Post marketing surveillance does not suggest an effect of tramadol on fertility.
Animal studies did not show an effect of tramadol on fertility.
No study in 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 operate machinery.

4.8 Undesirable effects

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

Cardiovascular system disorders:

Uncommon (may affect up to 1 in 100 people):

- palpitations
- tachycardia
- arrhythmia.

Ear and labyrinth disorders:

Uncommon (may affect up to 1 in 100 people)

- tinnitus.

Nervous system disorders:

Very common (may affect more than 1 in 10 people):

- dizziness,
- somnolence Not known:
- serotonin syndrome

Common (may affect up to 1 in 10 people):

- headache
- trembling.

Uncommon (may affect up to 1 in 100 people):

- involuntary muscular contractions
- paraesthesia
- amnesia.

Rare (may affect up to 1 in 1000 people):

- ataxia
- convulsions
- syncope
- speech disorders.

Psychiatric disorders:

Common (may affect up to 1 in 10 people):

- confusion
- mood changes (anxiety, nervousness, euphoria)
- sleep disorders.

Uncommon (may affect up to 1 in 100 people):

- depression
- hallucinations
- nightmares.

Rare (may affect up to 1 in 1000 people):

- drug dependence
- delirium.

Post marketing surveillance
Very rare (may affect up to 1 in 10,000 people):

- abuse.

Eye disorders:

Rare (may affect up to 1 in 1000 people):

- blurred vision
- miosis
- mydriasis.

Respiratory system disorders:

Uncommon (may affect up to 1 in 100 people):

- dyspnoea.

Not known:

- hiccups

Gastro-intestinal disorders:

Very common (may affect more than 1 in 10 people):

- nausea.

Common (may affect up to 1 in 10 people):

- vomiting
- constipation
- dry mouth
- diarrhoea
- abdominal pain
- dyspepsia
- flatulence.

Uncommon (may affect up to 1 in 100 people):

- dysphagia
- melaena.

Investigations:

Uncommon (may affect up to 1 in 100 people):

- hepatic transaminases increase.

Skin and appendages disorders:

Common (may affect up to 1 in 10 people):

- hyperhidrosis (sweating)
- pruritus.

Uncommon (may affect up to 1 in 100 people):

- dermal reactions (e.g. rash, urticaria).

Urinary system disorders:

Uncommon (may affect up to 1 in 100 people):

- albuminuria
- micturition disorders (dysuria and urinary retention).

General disorders and administrative site conditions:

Uncommon (may affect up to 1 in 100 people):

- chills thoracic pain.

Metabolism and nutrition disorders

Not known (cannot be estimated from available data):

- hypoglycaemia
- High anion gap metabolic acidosis.

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Vascular disorders

Uncommon (may affect up to 1 in 100 people):

- hypertension
- hot flushes.

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.

Rare cases (may affect up to 1 in 1000 people):

- allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema)
- anaphylaxis.

Rare cases (may affect up to 1 in 1000 people):

- changes in appetite

- motor weakness
- 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 elation occasionally dysphoria)
- changes in activity (usually suppression occasionally increase)
- 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 withdrawal reactions, similar to those occurring during opiate withdrawal may occur as follows:

- agitation
- anxiety

- nervousness
- insomnia
- hyperkinesia
- tremor
- gastrointestinal symptoms.

Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

Paracetamol

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

Drug dependence
Repeated use of Tramadol/Paracetamol Rowa can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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

***Risk of overdose with paracetamol*:**
There is a risk of poisoning with paracetamol particularly in elderly subjects, young children, patients with liver disease, cases of chronic alcoholism and in patients with chronic malnutrition. Overdosing may be fatal in these cases.
Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol in a single administration in adults or in children can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk Factors include:
If the patient;

- Is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Regularly consumes ethanol in excess of recommended amounts
- Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Emergency Procedure:
Immediate transfer to hospital.
Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if>150 mg/kg paracetamol has been taken within 1 hour.
The antidote N-acetylcysteine, should be administered as soon as possible in accordance with National treatment guidelines.
Symptomatic treatment should be implemented.

Symptoms of overdose from tramadol:
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 up to coma, convulsions and respiratory depression up to respiratory arrest. Serotonin syndrome has also been reported.

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 overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.
- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.
- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment of acute intoxication with Tramadol/Paracetamol Rowa with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tramadol, combinations ATC code: N02AJ13

ANALGESICS

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non selective agonists of the μ, 8, and K opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastro-intestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

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

Tramadol/paracetamol is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the 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 administration of a tramadol/paracetamol (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 ng/ml[(+)-tramadol/(-)-tramadol] and 4.2 μg/ml (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)- tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives t1/2 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 clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

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

After administration of tramadol/paracetamol, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol.

The oral administration of Tramadol/Paracetamol Rowa with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that Tramadol/Paracetamol Rowa can be taken independently of meal times.

Distribution:
Tramadol has a high tissue affinity (V d,β = 203 ±40 1). 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 is extensively metabolized after oral administration. About 30 % of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolite.

Tramadol is metabolised through *O*-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1 and through *N*-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N- demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties

and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect is unlikely to change on multiple dosing.

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.

Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P 450 to an active intermediate (the N-acetyl benzoquinone imine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

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

5.3 Preclinical safety data

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

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

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

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

Animal studies with tramadol revealed, at very high doses, effects on organ development, ossification and neonatal mortality, associated with materno-toxicity. Fertility reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. No effect on fertility has been observed after oral administration of tramadol up to doses of 50 mg/kg in the male rat and 75 mg/kg in the female rat.

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Pregelatinised maize starch
Stearic acid
Povidone K
Croscarmellose sodium

Film-coating:

Opadry light yellow containing:
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Polyethylene glycol
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Tramadol/Paracetamol Rowa tablets are packed in aluminium-PVC blisters.
The blisters are packed in carton boxes in pack sizes of 20, 60 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Limited
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0074/070/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th July 2017
Date of last renewal: 6th July 2022

10 DATE OF REVISION OF THE TEXT

January 2025