

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Tradol Plus 37.5 mg/325 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 37.5 mg of tramadol hydrochloride and 325 mg of paracetamol.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.

White, scored tablet of oblong shape (15 x 6.5 mm).

The score line is not intended for breaking the tablet.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Tradol Plus tablets are indicated for the symptomatic treatment of moderate to severe pain.

The use of Tradol Plus 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

The use of Tradol Plus 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 the 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 tramadol hydrochloride and 2600 mg paracetamol) per day should not be exceeded. The dosing interval should not be less than six hours.

#### *Adults and adolescents (12 years and older)*

An initial dose of two tablets of Tradol Plus 37.5 mg/325 mg is recommended. Additional doses 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/paracetamol 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 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 has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

#### *Elderly*

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 impairment/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.

In patients with moderate renal insufficiency (glomerular filtration rate 10-50 ml/min), the dose of paracetamol should be reduced (maximum daily dose 2000 mg).

#### *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, Tradol Plus should not be used in patients with severe hepatic impairment (see section 4.3).

In patients with impaired hepatic function or Gilbert's syndrome, the dose of paracetamol must be reduced or the dosing interval prolonged.

#### Method of administration

Oral use.

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

### **4.3 Contraindications**

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Acute intoxication with alcohol, hypnotic medicinal products, centrally-acting analgesics, opioids or psychotropic medicinal products
- Tradol Plus must not be administered to patients who are receiving 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

- In adults and adolescents 12 years and older, the maximum dose of 8 tablets a day of Tradol Plus 37.5 mg/325 mg should not be exceeded (equivalent to 300 mg of tramadol hydrochloride and 2600 mg of paracetamol). In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other medicinal products containing paracetamol (including over-the-counter medicinal products) or tramadol hydrochloride concurrently without the advice of a physician.
- In severe renal insufficiency (creatinine clearance < 10 ml/min), tramadol/paracetamol is not recommended.
- In patients with severe hepatic impairment, Tradol Plus must 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.
- In severe respiratory insufficiency, tramadol/paracetamol 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 anaesthetics. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with tramadol/paracetamol 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).

*Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products*

Concomitant use of tramadol/paracetamol and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe tramadol/paracetamol concomitantly with sedative medicinal products 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 adverse reactions 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:

<b>Population</b>	<b>Prevalence %</b>
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 for use

Tolerance, psychic and physical dependence may develop, especially after long-term use. 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 period and under medical supervision.

Tramadol/paracetamol 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.

Paracetamol in overdose may cause hepatic toxicity in some patients.

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

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

#### 4.5 Interaction with other medicinal products and other forms of interactions

##### Tramadol

*Concomitant use is contraindicated with:*

##### **Non-selective MAO inhibitors**

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

##### **Selective-AMAO inhibitors**

Extrapolation from non-selective MAO inhibitors

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

##### **Selective-BMAO inhibitors**

Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

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

*Concomitant use is not recommended with:*

##### **Alcohol**

Alcohol increases the sedative effect of opioid analgesics.

The effect on alertness can make driving of vehicles and the use of machines dangerous.

Avoid intake of alcoholic drinks and of 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 medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and **serotonergic medicinal products**, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin toxicity.

Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis

- Tremor and hyperreflexia
- Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotonergic medicinal products usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

**Other opioid derivatives (including antitussive medicinal products and substitutive treatments) and barbiturates**

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

**Sedative medicinal products such as benzodiazepines or related medicinal products**

The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products 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).

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

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

As medically appropriate, periodic evaluation of prothrombin time should be performed when tramadol/paracetamol 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-HT<sub>3</sub> antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

Paracetamol

As medically appropriate, periodic evaluation of prothrombin time should be performed when tramadol/paracetamol and warfarin like compounds are administered concurrently due to reports of increased INR

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. Cholestyramine should not be given within one hour of administration of paracetamol in order to achieve maximum analgesic effect.

Isoniazid affects the pharmacokinetics of paracetamol with possible potentiation of liver toxicity.

Probenecid inhibits the binding of paracetamol to glucuronic acid, thus leading to a reduction in paracetamol clearance by a factor of approximately 2. In patients concurrently taking probenecid, the paracetamol dose should be reduced.

Use of substances that induce liver enzymes, such as carbamazepine, phenytoin, phenobarbital, rifampicin and St John's wort (*Hypericum perforatum*) can increase the hepatotoxicity of paracetamol due to increased and more rapid formation of toxic metabolites. Therefore, caution should be taken in case of concomitant use of enzyme inducing substances.

Paracetamol may affect the pharmacokinetic of chloramphenicol. Monitoring of chloramphenicol plasma concentrations is recommended if combining paracetamol with chloramphenicol injection treatment.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

Since Tradol Plus is a fixed combination of active substances including 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. Paracetamol can be used during pregnancy if clinically needed 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 induce changes in the respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to neonatal withdrawal symptoms.

##### Breast-feeding

Since Tradol Plus is a fixed combination of active substances including tramadol, it should not be used during breast-feeding.

##### *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*

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 dose. 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. 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 central nervous system (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 a tramadol/ paracetamol combination were nausea, dizziness and somnolence, observed in more than 10% of the patients.

The frequencies are defined as follows:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Verycommon	Common	Uncommon	Rare	Very rare	Frequency not known
<b>Metabolism and nutrition disorders</b>						Hypoglycaemia
<b>Psychiatric disorders</b>		Confusional state, mood altered (anxiety, nervousness, euphoric mood), sleep disorders	Depression, hallucination, nightmares	Delirium, drug dependence	Abuse	
<b>Nervous system disorders</b>	Dizziness, somnolence	Headache, trembling	Involuntary muscular contractions, paraesthesia, amnesia	Ataxia, convulsions, syncope, speech disorders		
<b>Eye disorders</b>				Vision blurred, miosis, mydriasis		
<b>Ear and labyrinth disorders</b>			Tinnitus			
<b>Cardiac disorders</b>			Palpitations, tachycardia, arrhythmia			
<b>Vascular disorders</b>			Hypertension, hot flush			
<b>Respiratory, thoracic and mediastinal disorders</b>			Dyspnoea			
<b>Gastrointestinal disorders</b>	Nausea	Vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence	Dysphagia, melaena			
<b>Skin and subcutaneous tissue disorders</b>		Hyperhidrosis, pruritus	Dermal reactions (e.g. rash, urticaria)			
<b>Renal and urinary disorders</b>			Albuminuria, micturition disorders (dysuria and urinary			

			retention)			
<b>General disorders and administration site conditions</b>			Chills, chest pain			
<b>Investigations</b>			Transaminases increased			

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

#### Tramadol

- Postural hypotension, bradycardia, collapse
- Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
- Rare: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
- Rare: changes in appetite, motor weakness, and respiratory depression.

Psychic side-effects may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually euphoric mood occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders).

Worsening of asthma has been reported, though a causal relationship has not been established.

Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

Other symptoms that have 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 hypoprothrombinaemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

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](http://www.hpra.ie).

## 4.9 Overdose

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

### 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.

### Symptoms of overdose from paracetamol

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 of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Liver damage is possible in adults who have taken 7.5-10g 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 overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform liver function tests.
- Perform liver 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 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 instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment of acute intoxication with tramadol/paracetamol with haemodialysis or haemofiltration alone is not suitable for detoxification.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any adult or adolescent who had ingested around 7.5 g or more of paracetamol in the preceding 4 hours or any child who has ingested  $\geq 150$  mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage.

Paracetamol concentrations in blood should be measured later than 4 hours after overdose 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 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when massive overdose is suspected. General supportive measures must be available.

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids in combination with non-opioid analgesics ATC code: N02AJ13

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non selective agonists of the  $\mu$ ,  $\delta$  and  $\kappa$  and opioid receptors with a higher affinity for the  $\mu$  receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastrointestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

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

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

#### Paediatric population

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2,000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year.

## **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 microgram/ml [(+)-tramadol/(-)-tramadol] and 4.2 microgram/ml (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. 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 clinical significant change was observed in the kinetic parameters of each active substance compared to the parameters of the active substance used alone.

#### Absorption

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

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

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

#### Distribution

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

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

### Biotransformation

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

Tramadol is metabolised through O-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through N-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect is unlikely to change on multiple dosing.

Paracetamol is principally metabolised in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to an active intermediate (the N-acetyl 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.

### Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol has been investigated, but has not been fully characterised. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

## **5.3 Preclinical safety data**

### Tramadol/paracetamol

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 hydrochloride/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 hydrochloride/paracetamol) did not result in toxic effects in the embryo or the foetus.

### Tramadol

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 maternotoxicity. Fertility reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. Male and female fertility was not affected.

### Paracetamol

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.

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**

Povidone K 29/32  
Magnesium stearate  
Colloidal anhydrous silica  
Sodium starch glycolate (Type A)  
Pregelatinised maize starch.

### **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**

Tradol Plus tablets are packed in aluminium/polyethylene strips or aluminium/PVC-PVDC blisters.  
Tradol Plus 37.5 mg/325 mg tablets: Packs of 2, 10, 20, 30, 40, 50, 60, 90 and 100 tablets.  
(The pack size 100 is limited for hospital use.)

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Rowex Ltd  
Newtown  
Bantry  
Co. Cork  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0711/256/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of First Authorisation: 12<sup>th</sup> February 2016  
Date of latest renewal: 27<sup>th</sup> March 2018

**10 DATE OF REVISION OF THE TEXT**

June 2020