Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramadol/Paracetamol Krka 37.5mg/325mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 37.5 mg tramadol hydrochloride equivalent to 32.94 mg tramadol and 325 mg paracetamol.

Excipient with known effect
Each film-coated tablet contains 1.25 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Tablets are yellow-brown, oval, slightly biconvex.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

The use of Tramadol/Paracetamol Krka 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 Tramadol/Paracetamol Krka 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 tramadol hydrochloride and 2 600 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 Tramadol/Paracetamol Krka is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol hydrochloride and 2 600 mg paracetamol) per day.
The dosing interval should not be less than six hours.

Tramadol/Paracetamol Krka 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 Krka 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 Krka 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
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.

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/Paracetamol Krka should not be used in patients with severe hepatic impairment (see section 4.3).

Method of administration
Oral use.
Tablets must be swallowed whole, with a sufficient quantity of liquid. They must 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 intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs.
Tramadol/Paracetamol Krka 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 and older. The maximum dose of 8 tablets of Tramadol/Paracetamol Krka 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.
- In severe renal insufficiency (creatinine clearance <10 ml/min), Tramadol/Paracetamol Krka is not recommended.
- In patients with severe hepatic impairment Tramadol/Paracetamol Krka 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.
- In severe respiratory insufficiency, Tramadol/Paracetamol Krka 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 Krka 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 apnea (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.

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.

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.

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.

Precautions for use

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

Concomitant use of Tramadol/Paracetamol Krka 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 Krka concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of the concomitant treatment should be as short as possible.

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.

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).

Tolerance and physical and/or psychological dependence may develop, 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 period and under medical supervision.

Tramadol/Paracetamol Krka 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 center or the respiratory function, or with an increased intracranial pressure.

Paracetamol in overdosage 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). Withdrawal symptoms may be avoided by taper 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 plans of anaesthesia should be avoided.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, 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 MAO Inhibitors*

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

- *Selective-A MAO Inhibitors*Extrapolation from non-selective MAO inhibitors.Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.
- *Selective-B MAO 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 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). 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), 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.
- Sedating medicinal products such as benzodiazepines or related substances: 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 effects. The dose and duration of the concomitant use should be limited (see section 4.4).
- As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol/Paracetamol Krka 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 risk factors (see section 4.4).

4.6 Fertility, pregnancy and lactation

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

Data regarding paracetamol:
Studies in animals are insufficient to conclude on reproductive toxicity. 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.

Data regarding tramadol:
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.

Breast-feeding
Since Tramadol/Paracetamol Krka is a fixed combination of active ingredients including tramadol, it should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with Tramadol/Paracetamol Krka. Discontinuation of breast-feeding is generally not necessary following a single dose of Tramadol/Paracetamol Krka.

Data regarding paracetamol:
Paracetamol is excreted in breast milk but not in a clinically significant amount.

Data regarding tramadol:
Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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

The frequencies are defined as follows:

- 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)
- unknown (Frequency cannot be estimated from the available data)

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

Frequency of undesirable effects listed by individual organ systems:

	Very common	Common	Uncommon	Rare	Very rare	Unknown
Metabolism and nutrition disorders						hypoglycaemia
Psychiatric disorders		confusional state, mood altered (anxiety, nervousness, euphoric mood), sleep disorders	depression, hallucinations, nightmares	delirium, drug dependence	abuse*	

Nervous system disorders	dizziness, somnolence	headache, trembling	involuntary muscular contractions, paraesthesia, amnesia	ataxia, convulsions, syncope, speech disorders		
Eye disorders				vision blurred, miosis, mydriasis		
Ear and labyrinth disorders			tinnitus			
Cardiac disorders			palpitations, tachycardia, arrythmia			
Vascular disorders			hypertension, hot flush			
Respiratory, thoracic and mediastinal disorders			dyspnoea			
Gastrointestinal disorders	nausea	vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence	dysphagia, melaena			
Skin and subcutaneous tissue disorders		hyperhidrosis, pruritus	dermal reactions (e.g.rash, urticaria)			
Renal and urinary disorders			albuminuria, micturition disorders (dysuria and urinary retention)			
General disorders and administration site conditions			chills, chest pain			
Investigations			transaminases increase			

*Reported in post marketing surveillance.

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 (≥ 1/10 000 to < 1/1 000): allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
- Rare cases (≥ 1/10 000 to < 1/1 000): 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.

- Nervous system disorders: Not known: Serotonin syndrome.
- 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.
- Respiratory, thoracic and mediastinal disorders: frequency not known: hiccups.

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.
- Metabolism and nutrition disorders: cases of pyroglutamic acidosis (PGA) were reported with frequency not known, when paracetamol is used alone or with concomitant treatment of flucloxacillin, especially in patients with risk factors and prolonged treatment (see sections 4.4 and 4.5).

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 Krka 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.

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.

Symptoms of overdose from paracetamol
An overdose is of particular concern in young children. Symptoms of paracetamol overdosage 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 7.5-10 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 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 Krka 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 ≥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, tramadol and paracetamol, ATC code: N02AJ13.

Analgesics
Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure nonselective agonist of the μ, δ, and κ 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 Krka 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 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 the fixed-dose tramadol/paracetamol combination, no clinically significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

<u>Absorption</u>

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 Tramadol/Paracetamol Krka can be taken independently of meal times.

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

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

Biotransformation
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 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 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 P450 to an active intermediate (the N-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Elimination
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

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 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 maternotoxicity. Fertility reproductive performance and development of offspring were unaffected. *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 dosages of *paracetamol*.

Animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Pregelatinised maize starch
Sodium starch glycolate (type A)
Microcrystalline cellulose (E460)
Magnesium stearate (E470b)

Film-coating
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Yellow iron oxide (E172)
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

Blister (PVC/PVDC white foil, aluminium foil): 2 film-coated tablets (blisters with 2 tablets) or 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 film-coated tablets (blisters with 10 tablets), in a box.

Child-resistant blister (PVC/PVDC white foil, paper/aluminium foil): 2 film-coated tablets (blisters with 2 tablets) or 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 film-coated tablets (blisters with 10 tablets), in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/052/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd January 2015
Date of last renewal: 5th December 2019

10 DATE OF REVISION OF THE TEXT

May 2024