

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tramadol/Paracetamol 75 mg / 650 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 75 mg of tramadol hydrochloride and 650 mg of paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White, elongated, scored tablets.

For doses of 75 mg /650 mg, the tablet can be divided into equal doses.

4.1 Therapeutic indications

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

The use of Tramadol/Paracetamol 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:

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with tramadol hydrochloride in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Adults and adolescents (12 years and older).

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

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

An initial dose of two tablets of Tramadol/Paracetamol 37.5 mg / 325 mg or one tablet of Tramadol/Paracetamol 75 mg / 650 mg is recommended.

Additional doses can be taken as needed, not exceeding 8 tablets of Tramadol/Paracetamol 37.5 mg / 325 mg or 4 tablets of Tramadol/Paracetamol 75 mg / 650 mg (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 Section 4.4 - Special warnings and precautions for use). 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 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 the dosage interval is to be extended according to the patient's requirements.

The usual dosages may be used, although it should be noted that in volunteers aged over 75 years the elimination half-life of tramadol was increased by 17% following oral administration. In patients over 75 years old, it is recommended that the minimum interval between doses should not be less than 6 hours, due to the presence of tramadol.

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 requirement.

Due to the presence of tramadol, the use of Tramadol/Paracetamol is not recommended in patients with severe renal failure (creatinine clearance < 10 ml/min). In cases of moderate renal failure (creatinine clearance between 10 and 30 ml/min), the dosing should be increased to 12-hourly intervals. As tramadol is removed only very slowly by haemodialysis or by haemofiltration, post-dialysis administration to maintain analgesia is not usually required.

Hepatic insufficiency

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

Method of administration:

Oral use

Tablets must be swallowed with a sufficient quantity of liquid.

The score line is only to facilitate the breaking of the tablet for easy swallowing.

Treatment goals and discontinuation

Before initiating treatment with Tramadol/Paracetamol, 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 the active substances or to any of the excipients listed in section 6.1,
- acute intoxication with alcohol, hypnotic drugs or centrally acting analgesics, opioids or psychotropic drugs,
- this medicinal product 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 (equivalent to 300 mg of tramadol and 2600 mg of paracetamol) of 8 tablets a day of Tramadol/Paracetamol 37.5 mg / 325 mg or 4 tablets of Tramadol/Paracetamol 75 mg / 650 mg 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 is not recommended.
- In patients with severe hepatic impairment Tramadol/Paracetamol 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 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 medicines that lower the seizure threshold, especially selective serotonin reuptake 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 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).
- 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.

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.

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.

CYP2D6 metabolism

Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing <side effects> of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

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

Post-operative use in children

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

Children with compromised respiratory function

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

Precautions for use:

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

Concomitant use of Tramadol/Paracetamol 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 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).

Tramadol hydrochloride/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.

A paracetamol overdose can cause hepatic toxicity in some patients.

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.

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Tramadol/Paracetamol. Repeated use of Tramadol/Paracetamol can lead to opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Tramadol/Paracetamol 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 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.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with tramadol hydrochloride.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

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 MAO inhibitors**

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

- **Selective-A MAO inhibitors**

Extrapolation from non-selective MAO inhibitors

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

- **Selective-B MAO inhibitors**

Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, and 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 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 re-uptake 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.

- 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)

Sedating medicinal products such as benzodiazepines or related substances:

The concomitant use of opioids with sedative medicines such as benzodiazepines, gabapentinoids (gabapentin and pregabalin) or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

Since Tramadol/Paracetamol 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 fetoneonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

- **Data regarding tramadol:**

Tramadol should not be used during pregnancy, as there is inadequate evidence available to assess the safety of tramadol in pregnant women. Tramadol administered before or during birth does not affect uterine contractility. In neonates it may 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.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding:

Since this medicine is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

Administration to nursing women is not recommended as tramadol may be secreted in breast milk and may cause respiratory depression in the infant.

*** Data on 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.

*** Data on 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 central nervous system (CNS) depressants. If affected, the patient should not drive or operate machinery.

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

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

4.8 Undesirable effects

The most commonly reported undesirable effects during the clinical trials performed with the paracetamol/ tramadol combination were nausea, dizziness and somnolence, which were 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: $\geq 1/1000$ to $< 1/100$

Rare: $\geq 1/10\ 000$ to $< 1/1000$

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.

Cardiac disorders:

Uncommon: palpitations, tachycardia, arrhythmia.

Eye disorders:

Rare: vision blurred, miosis, mydriasis

Ear and labyrinth disorders:

Uncommon: tinnitus

Gastrointestinal disorders:

Very common: nausea,

Common: vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence.

Uncommon: dysphagia, melaena.

General disorders and administration site conditions:

Uncommon: chills, chest pain, drug withdrawal syndrome

Investigations:

Uncommon: transaminases increased

Metabolism and nutrition disorders:

Unknown: hypoglycaemia

Nervous system disorders:

Very common: dizziness, somnolence

Common: headache, trembling

Uncommon: involuntary muscular contractions, paraesthesia, amnesia

Rare: ataxia, convulsions, syncope, speech disorders.

Unknown: Serotonin syndrome

Psychiatric disorders:

Common: confusional state, mood altered, anxiety, nervousness, euphoric mood, sleep disorders

Uncommon: depression, hallucinations, nightmares

Rare: delirium,

Frequency unknown: Drug dependence (see section 4.4)

Post marketing surveillance

Very rare: abuse.

Renal and urinary disorders:

Uncommon: albuminuria, micturition disorders (dysuria and urinary retention)

Respiratory, thoracic and mediastinal disorders:

Uncommon: dyspnoea

Frequency unknown: hiccups

Skin and subcutaneous tissue disorders:

Common: hyperhidrosis, pruritus

Uncommon: dermal reactions (e.g. rash, urticaria).

Vascular disorders:

Uncommon: hypertension, hot flush

Although not observed during clinical trials, the occurrence of the following undesirable effects 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 in prothrombin times.
- Rare cases ($\geq 1/10,000$ to $< 1/1,000$): allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
- Rare cases ($\geq 1/10,000$ 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 the 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.

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 they 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.
- 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)

Drug dependence

Repeated use of Tramadol/Paracetamol 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 professional are asked to report any suspected adverse reactions via the Yellow Card Scheme (website: www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms of an 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 including coma, convulsions and respiratory depression, including 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 arrhythmia 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 excessive 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 the 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 may be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment with 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 taking ≥ 150 mg/kg of paracetamol in the preceding 4 hours, should undergo gastric lavage.

Paracetamol concentrations in blood should be measured more than 4 hours after an 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-acetyl cysteine (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 a 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: tramadol and paracetamol.

ATC code: N02AJ13

ANALGESICS

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure, non-selective agonist of the μ , δ and κ opioid receptors, with a higher affinity for μ receptors. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

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

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

Tramadol/Paracetamol is positioned as a Class II analgesic on the WHO pain ladder and should be utilised accordingly by physicians.

5.2 Pharmacokinetic properties

Tramadol is administered as a racemic and both 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 is longer) than that of paracetamol.

After a single oral administration of a tablet of tramadol/paracetamol (37.5 mg/325 mg), peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 μ g/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 performed on healthy volunteers, after single and repeated oral administrations of Tramadol/Paracetamol, no significant clinical changes were seen in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

Absorption:

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

After the 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.

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; therefore, Tramadol/Paracetamol can be taken independently of meal times.

Distribution:

Tramadol has a high tissue affinity ($V_{d\beta}=203 \pm 40$ l). Plasma protein binding is 20%.

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

Metabolism:

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

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

Paracetamol is principally metabolised mainly in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses that are higher than the therapeutic dose. A small fraction (less than 4%) is metabolised by the cytochrome, P450, to an active intermediate product (N-acetyl benzoquinoneimine), which, under normal conditions of use, is readily detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, in cases of massive overdose, the quantity of this metabolite is increased.

Elimination:

Tramadol and its metabolites are cleared mainly by the kidneys. The half-life of paracetamol is about 2 to 3 hours in adults. It is shorter in children and slightly longer in newborns and cirrhotic patients. Paracetamol is mainly eliminated by the dose-dependent formation of glucuro-conjugated and sulpho-conjugated 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 this medicine has been observed in the progeny of rats treated orally with the combination of tramadol/paracetamol.

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

The combination tramadol/paracetamol has been proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg of 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 effects on 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.

The results of carcinogenicity tests do not suggest a potential risk of tramadol in 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. 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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (E1201), magnesium stearate (E572), anhydrous colloidal silica, sodium starch glycolate (type A) and 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

Tramadol/Paracetamol tablets are packed in aluminium-polyethylene strips or aluminium/ PVC-PVDC blisters.

Tramadol/Paracetamol 75 mg / 650 mg tablets: Packs contain 2, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The disposal of any unused drug and all materials that come into contact with it will be performed according to local regulations (or such can be returned to the pharmacy).

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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