SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Yellow coloured, elongated, film-coated tablet with “325” debossed on one side and ‘‘37.5’’ debossed on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Posology

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

The dose should be adjusted according 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 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 Tramadol hydrochloride and Paracetamol tablets is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 2600 mg paracetamol and 300 mg tramadol) per day. The dosing interval should not be less than six hours.

Tramadol hydrochloride and Paracetamol tablets should under no circumstances be administered for longer than is strictly necessary (see also section 4.4 - Special warnings and precautions for use). If repeated use or long term treatment with Tramadol hydrochloride and Paracetamol tablets 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 hydrochloride and Paracetamol tablets has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

Special populations

Elderly patients
A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In older people 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 insufficiency
In patients with severe 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 and Paracetamol tablets 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.

Treatment goals and discontinuation
Before initiating treatment with Tramadol hydrochloride and Paracetamol tablets, 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 paracetamol, tramadol or to any of the excipients (see section 6.1) of the medicinal product
- Acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs
- Tramadol hydrochloride and Paracetamol tablets 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 hydrochloride and Paracetamol tablets 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/mm), Tramadol hydrochloride and Paracetamol tablets is not recommended.

In patients with severe hepatic impairment Tramadol hydrochloride and Paracetamol tablets 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 hydrochloride and Paracetamol tablets are 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 hydrochloride and Paracetamol tablets 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).

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

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.

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 hydrochloride and Paracetamol tablets with 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 drugs should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol hydrochloride and Paracetamol tablets concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of the concomitant treatment should be as short as possible.

Tolerance, psychic and physical dependence may develop, even at therapeutic doses and especially after long-term use. The clinical need for analgesic treatment should be reviewed regularly (see section 4.2). Tramadol hydrochloride and Paracetamol tablets should be used with caution in opioid dependent patients, or 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.

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 hydrochloride and Paracetamol tablets. Repeated use of Tramadol hydrochloride and Paracetamol tablets 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 hydrochloride and Paracetamol tablets 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 hydrochloride and Paracetamol tablets 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.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal insufficiency

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

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status change, 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.

Excipients

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

- Selective-A MAO Inhibitors

Extrapolation from non-selective MAO inhibitors.

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

- Selective-B MAO Inhibitors

Central excitation symptoms evocative of a serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

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

Concomitant use is not recommended with:

- Alcohol

Alcohol increases the sedative effect of opioid analgesics.

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

Avoid intake of alcoholic drinks and of medicinal products containing alcohol.

- Carbamazepine and other 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), benzodiazepines and barbiturates increase risk of respiratory depression which can be fatal in cases of overdose.
- Other central nervous system depressants, such as other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen.

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

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).

The concomitant use of Tramadol hydrochloride and Paracetamol tablets with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol hydrochloride/Paracetamol tablets and warfarin like compounds are administered concurrently due to reports of increased INR.

Other drugs known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.

Medicinal products reducing the seizure threshold, such as bupropion, serotonin reuptake inhibitor antidepressants, tricyclic antidepressants and neuroleptics. Concomitant use of tramadol with these drugs can increase the risk of convulsions. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

In a limited number of studies, pre- or postoperative application of 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 due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

4.6 Fertility, pregnancy and lactation

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 preclinical study has been performed with the fixed combination (paracetamol and tramadol) to evaluate its effects on fertility. (see section 5.3)

Pregnancy
Since this medicine is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

Breast-feeding
Since Tramadol hydrochloride and Paracetamol tablet 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 hydrochloride and Paracetamol Tablets. Discontinuation of breast feeding is generally not necessary following a single dose of Tramadol hydrochloride and Paracetamol tablets.

Data regarding paracetamol:
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient medicinal products containing only paracetamol.

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

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.

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

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - o The medicine has been prescribed to treat a medical or dental problem and
    - o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - o 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 and tramadol combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients. *Cardiac disorders:*

- Uncommon (≥ 1/1000 to < 1/100): palpitations, tachycardia, arrythmia.

Nervous system disorders:

- Very common (≥ 1/10): dizziness, somnolence
- Common (≥ 1/100 to < 1/10): headache trembling
- Uncommon (≥ 1/1000 to < 1/100): involuntary muscular contractions, paraesthesia, amnesia
- Rare (≥ 1/10000 to < 1/1000): ataxia, convulsions, syncope.
- Not known (frequency cannot be estimated from the available data): Serotonin syndrome

Psychiatric disorders:

- Common (≥ 1/100 to < 1/10): confusional state, mood altered, anxiety, nervousness, euphoric mood, sleep disorders
- Uncommon (≥ 1/1000 to < 1/100): depression, hallucinations, nightmares
- Rare (≥ 1/10000 to < 1/1000): delirium, drug dependence.

Post marketing surveillance:

- very rare (< 1/10000): abuse.

Eye disorders:

- Rare (≥ 1/10000 to < 1/1000): blurred vision, miosis, mydriasis

Ear disorders:

- Uncommon (≥ 1/1000 to < 1/100): tinnitus

Investigations:

- Uncommon (≥ 1/1000 to < 1/100): transaminases increased

Respiratory, thoracic and mediastinal disorders:

- Uncommon (≥ 1/1000 to < 1/100): dyspnoea

Gastrointestinal disorders:

- Very common (≥ 1/10): nausea
- Common (≥ 1/100 to < 1/10): vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence
- Uncommon (≥ 1/1000 to < 1/100): dysphagia, melaena.

Liver and biliary system disorders:

- Uncommon (≥ 1/1000 to < 1/100): hepatic transaminases increase.

Skin and subcutaneous tissue disorders:

- Common (≥ 1/100 to < 1/10): hyperhidrosis, pruritus
- Uncommon (≥ 1/1000 to < 1/100): dermal reactions (e.g. rash, urticaria).

Urinary system disorders:

- Uncommon (≥ 1/1000 to < 1/100): albuminuria, micturition disorders (dysuria and urinary retention).

General disorders and administration site conditions:

- Uncommon (≥ 1/1000 to < 1/100): chills, chest pain

Metabolism and nutrition disorders:

- Unknown (≥ 1/1000 to < 1/100): hypoglycaemia, high anion gap metabolic acidosis

Renal and urinary disorders:
- Uncommon (≥ 1/1000 to < 1/100): albuminuria, micturition disorders (dysuria and urinary retention)

Vascular disorders:
- Uncommon (≥ 1/1000 to < 1/100): hypertension, hot flush

Drugs dependence
Repeated use of Tramadol hydrochloride and Paracetamol tablets 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).

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 (≥1/10000 to <1/1000): allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
- Rare cases (≥1/10000 to <1/1000): 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 withdrawal reactions, 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 - Not known (frequency cannot be estimated from the available data): hiccups

Paracetamol

- Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. Very rare cases of serious skin reactions 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.
- 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).

Description of selected adverse reactions
High anion gap metabolic acidosis

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

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Tramadol hydrochloride and Paracetamol tablet 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.

Serotonin syndrome has also been reported (see sections 4.4, 4.5 and 4.8).

Symptoms of overdose from tramadol

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.

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 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 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 hydrochloride/Paracetamol tablets 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tramadol, combinations

ATC code: N02AJ13

Analgesics

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non-selective agonists of the μ, 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 hydrochloride and Paracetamol tablet 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 paracetamol/tramadol (325 mg/37.5 mg) tablet, peak plasma concentrations of 4.2 μg/ml (paracetamol) and 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] are reached after 0.9 hour (paracetamol) and 1.8 hours [(+)-tramadol/(-)-tramadol] respectively. The mean elimination half-lives $t_{1/2}$ are 2.5 hours (paracetamol) and 5.1/4.7 hours [(+)-tramadol/(-)-tramadol] and 2,5 h (paracetamol.

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Tramadol hydrochloride and Paracetamol tablets, no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

Absorption

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

After administration of Tramadol hydrochloride and Paracetamol tablets, 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 hydrochloride and Paracetamol tablets with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that Tramadol hydrochloride and Paracetamol tablets 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 relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism

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

Tramadol is metabolised through O-demethylation (catalysed by enzyme CYP2D6) to metabolite M1 and through N-demethylation (catalysed by CYP3A) to 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 that 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 (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	**Film-coat (Opadry Yellow 15B82958)**
Pregelatinised starch Sodium starch glycolate (Type A) Microcrystalline cellulose Magnesium stearate Purified water	Hypromellose (3cP) Hypromellose (6cP) Titanium dioxide E171 Macrogol 400 Iron oxide yellow 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

Tramadol hydrochloride and Paracetamol tablets are packed in milky white PVC/PVDC and aluminium-PVC blisters available in cartons of 60 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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HA1 1XD

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PL 30684/0222

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