SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect: one film-coated tablet contains 3.6 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

6.4 mm x 15.5mm, yellow, oblong, biconvex, film coated tablet with "T" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

The use of Tramadol Hydrochloride/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

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/Paracetamol Tablets in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology

Adults and adolescents (12 years and older)

The use of Tramadol Hydrochloride/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 individually adjusted according to intensity of pain and 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.

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

Tramadol Hydrochloride/Paracetamol 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/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 Hydrochloride/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 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 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 whole, with a sufficient quantity of liquid. They must not be broken or chewed.

Treatment goals and discontinuation
Before initiating treatment with Tramadol Hydrochloride/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, centrally-acting analgesics, opioids or psychotropic drugs.
- Tramadol Hydrochloride/Paracetamol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see 4.5 Interactions with other medicinal products and other forms of interaction).
- Severe hepatic impairment.
- Epilepsy not controlled by treatment (see 4.4 Special Warnings).

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/Paracetamol 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/Paracetamol is not recommended.

- In patients with severe hepatic impairment Tramadol Hydrochloride/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 Hydrochloride/Paracetamol is not recommended.

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

- Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Tramadol Hydrochloride/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 Interactions with other medicinal products and other forms of interaction).

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.

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, 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 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 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 Hydrochloride/Paracetamolconcomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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 are 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.

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 opioid use disorder (abuse and dependence)

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

Before initiating treatment with Tramadol Hydrochloride/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 risk 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.

The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions. Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

Paracetamol in overdosage may cause hepatic toxicity in some patients.

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/Paracetamol.

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.

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.

After long term treatment (> 3 months) of analgesics with use every second day or more frequently, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

Tramadol Hydrochloride/Paracetamol Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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, hyperhidrosis, trembling, confusional state, even coma.

- Selective-A MAO Inhibitors

Extrapolation from non-selective MAO inhibitors
Risk of serotoninergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

- Selective-B MAO Inhibitors
  Central excitation symptoms evocative of a serotoninergic 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, triptans and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8.

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

- Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates. Increased risk of respiratory depression, which can be fatal in cases of overdose.

- Other central nervous system depressants, such as other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen. These drugs can cause increased central

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

- 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 sedative 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 Hydrochloride/Paracetamol 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 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 due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Since Tramadol Hydrochloride/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 foeto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

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.
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.
Tramadol administered before or during birth does not affect uterine contractility.
Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding
Since Tramadol Hydrochloride/Paracetamol 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/Paracetamol. Discontinuation of breast feeding is generally not necessary following a single dose of Tramadol/Paracetamol.

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

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. Alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of 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.

Fertility
Post marketing surveillance does not suggest any 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.

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:
  - 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, 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.

Cardiac disorders:
- Uncommon: palpitations, tachycardia, arrhythmia.

Nervous system disorders:
- Very common: dizziness, somnolence
- Common: headache trembling
- Uncommon: involuntary muscular contractions, paraesthesia, amnesia
- Rare: ataxia, convulsions, syncope, speech disorders.

Psychiatric disorders:
- Common: confusional state, mood altered (anxiety, nervousness, euphoric mood), sleep disorders
- Uncommon: depression, hallucinations, nightmares
- Rare: delirium, drug dependence (see section 4.4).

<u>Post marketing surveillance</u>
- Very rare: abuse.

Eye disorders:
- Rare: blurred vision, miosis, mydriasis

Ear and labyrinth disorders:

- Uncommon: tinnitus

Respiratory, thoracic and mediastinal disorders:
- Uncommon: dyspnoea
- Unknown: Hiccups

Gastro-intestinal disorders:
- Very common: nausea
- Common: vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence
- Uncommon: dysphagia, melaena.

Investigations:
- Uncommon: hepatic transaminases increase.

Skin and subcutaneous tissue disorders:
- Common: hyperhidrosis, pruritus
- Uncommon: dermal reactions (e.g. rash, urticaria).

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

General disorders and administration site conditions:
- Uncommon: chills, chest pain.

Metabolism and nutrition disorders:
- Unknown: hypoglycaemia, high anion gap metabolic acidosis

Vascular disorders:
- Uncommon: hypertension, hot flush.

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:

<u>Tramadol</u>
- 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.
- Nervous system disorders: Not known: serotonin syndrome.
- 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.
- General disorders and administration site conditions:
  Uncommon (≥ 1/1000 to < 1/100): drug withdrawal syndrome.
  Symptoms of drug 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: 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.
- Very rare cases of serious skin reactions have been reported
- 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.
- 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 Hydrochloride/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).

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; website:

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

4.9 Overdose

Tramadol Hydrochloride/Paracetamol is a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol hydrochloride 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 overdose from tramadol hydrochloride:

In principle, on intoxication with tramadol hydrochloride, 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:
The treating physician should refer to the current national guidance for the treatment of paracetamol overdose

- 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 normalises 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 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, or if there is any doubt over the timing of paracetamol ingestion, 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: 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, 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 gastrointestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

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

Tramadol Hydrochloride/Paracetamol is positioned as a step II analgesic by the WHO pain ladder and should be utilised accordingly as indicated 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 □g/ml (paracetamol), are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives t1/2 are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2.5 h (paracetamol).

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

Absorption

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

After administration of Tramadol Hydrochloride/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 1 hour and are not modified by concomitant administration of tramadol.

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

Distribution

Tramadol has a high tissue affinity (Vd, □ = 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.

Biotransformation

Tramadol is extensively metabolised 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 metabolised in the liver through two major hepatic routes: glucuronidation and sulfation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to an active intermediate (the N-acetyl-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 sulfo-conjugate derivatives. Less than 9% of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

5.3 Preclinical safety data

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

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

The combination tramadol/paracetamol has proven to be embryotoxic and fetotoxic in the rat at a 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 fetal 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. 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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Pre-gelatinised Maize Starch

Stearic acid

Crospovidone

Povidone (Plasdone K29-32)

Maize Starch

Croscarmellose sodium

Microcrystalline cellulose

Magnesium stearate (vegetable)

Film-coating:

Opadry yellow II OYL 22903 (Lactose monohydrate, Hypromellose 15cP, Titanium dioxide, Macrogol/Peg 4000, Talc, Iron oxide yellow)

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

2, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100.

PVC-PVdC/Aluminium blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/1043

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/01/2015

10 DATE OF REVISION OF THE TEXT

22/01/2025