

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramadol/Paracetamol Accord 37.5mg/325mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One effervescent tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol.

Excipients: Each effervescent tablet contains 0.33 mg of soya oil, 12.6 mg of sucrose and 10.06 mmol (or 231.49 mg) of sodium. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablet.

White to off-white, round, flat, bevelled-edge tablets and plain on both sides with mottled appearance and odour of orange.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tramadol/Paracetamol effervescent is indicated for the symptomatic treatment of moderate to severe pain.

The use of Tramadol/Paracetamol effervescent should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol hydrochloride and paracetamol (see also section 5.1). Tramadol/Paracetamol is indicated in adults and adolescents at the age of 12 years or older.

4.2 Posology and method of administration

Posology

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

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

The total dose of 8 tablets (equivalent to 300 mg tramadol hydrochloride and 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 effervescent tablets of Tramadol/Paracetamol effervescent (equivalent to 75 mg tramadol hydrochloride and 650 mg paracetamol) is recommended. Additional doses can be taken as needed, not exceeding 8 effervescent tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day.

The dosing interval should not be less than six hours.

Tramadol/Paracetamol effervescent should under no circumstances be administered for longer than is strictly necessary (see also section 4.4). If repeated use or long term treatment with Tramadol/Paracetamol effervescent is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Paediatric population

The effective and safe use of Tramadol/Paracetamol has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

Elderly

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency.

In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal impairment

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 (see also 4.4 section).

Hepatic impairment

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

Method of administration

Oral use

Effervescent tablets should be taken dissolved in glass of drinking water.

4.3 Contraindications

- Hypersensitivity to the active substances, to peanut or soya or to any of the excipients listed in section 6.1,
- acute intoxication with alcohol, hypnotic medicinal products, centrally-acting analgesics, opioids or psychotropic medicinal products,
- Tramadol/Paracetamol effervescent 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

- In adults and adolescents 12 years and older. The maximum dose of 8 tablets of Tramadol/Paracetamol effervescent 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 effervescent is not recommended.
- In patients with severe hepatic impairment Tramadol/Paracetamol effervescent is contraindicated (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 effervescent is not recommended.
- Tramadol hydrochloride is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol hydrochloride cannot suppress morphine withdrawal symptoms.
- Convulsions have been reported in tramadol hydrochloride -treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Tramadol/Paracetamol effervescent only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol hydrochloride at the recommended dose levels. The risk may be increased when doses of tramadol hydrochloride exceed the recommended upper dose limit.
- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5).
- CYP2D6 metabolism

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

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Sleep-related breathing disorders

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

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.

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

Concomitant use of Tramadol/Paracetamol effervescent 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 effervescent concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of the concomitant 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).

Tolerance and physical and/or psychological dependence may develop, even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly (see section 4.2). In opioid-dependent patients and patients with a history of drug abuse or dependence, treatment should only be for short period and under medical supervision. Tramadol/Paracetamol effervescent should be used with caution in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory center or the respiratory function, or with an increased intracranial pressure.

Paracetamol in overdose may cause hepatic toxicity in some patients.

Symptoms of withdrawal reaction, similar to those occurring during opiate withdrawal, may occur even at therapeutic doses and for short term treatment (see section 4.8). Withdrawal symptoms may be avoided by taper it at the time of discontinuation especially after long treatment periods. Rarely, cases of dependence and abuse have been reported (see section 4.8).

In one study, use of tramadol hydrochloride during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol hydrochloride during light planes of anaesthesia should be avoided.

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.

This medicinal product contains 231.49 mg of sodium per effervescent tablet, equivalent to 11.57% of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product (8 effervescent tablets) is equivalent to 92.56% of the WHO recommended maximum daily intake for sodium.

Tramadol/Paracetamol effervescent is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant use is contraindicated with:

- Non-selective MAO Inhibitors
Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.
- Selective-A MAO Inhibitors
Extrapolation from non-selective MAO inhibitors Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.
- Selective-B MAO Inhibitors
Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma. In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol hydrochloride.

(See also 4.3 section)

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 (see also 4.7 section). 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 (see 4.4 section).
- Concomitant therapeutic use of tramadol and serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).
- Other opioid derivatives (including antitussive medicinal products 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 medicinal products and substitutive treatments), other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive medicinal products, thalidomide and baclofen. These active substances can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous (see also 4.7 section).
- Sedating medicinal products such as benzodiazepines or related substances: the concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dose and duration of the concomitant use should be limited (see section 4.4)
- As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramadol/Paracetamol effervescent and warfarin like compounds are administered concurrently due to reports of increased INR, with significant bleeding and ecchymoses.
- In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT₃ antagonist ondansetron increased the requirement of tramadol hydrochloride in patients with postoperative pain.
- Other drugs known to inhibit CYP3A4, such as ketoconazole or erythromycin, may inhibit tramadol metabolism (N-demethylation) and possibly also metabolism active O-demethylated metabolite. The clinical significance of this interaction has not been studied.
- The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

4.6 Fertility, pregnancy and lactation*Pregnancy*

Since Tramadol/Paracetamol effervescent is a fixed combination of active substances including tramadol hydrochloride, it should not be used during pregnancy.

Data regarding paracetamol:

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Data regarding tramadol hydrochloride:

Tramadol hydrochloride should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol hydrochloride in pregnant women. Tramadol hydrochloride 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.

Breastfeeding

Since Tramadol/Paracetamol effervescent is a fixed combination of active ingredients including tramadol hydrochloride, it should not be used during breast feeding.

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 hydrochloride:

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 hydrochloride may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported undesirable effects during the clinical trials performed with the paracetamol/tramadol combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients.

The frequencies are defined as follows:

Very common: $\geq 1/10$

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.

Metabolism and nutrition disorders:

- Unknown: hypoglycaemia

Psychiatric disorders:

- Common: confusional state, mood altered (anxiety, nervousness, euphoric mood), sleep disorders
- Uncommon: depression, hallucination, nightmares,
- Rare: delirium, drug dependence.

Nervous system disorders:

- Very common: dizziness, somnolence
- Common: headache trembling
- Uncommon: involuntary muscular contractions, paraesthesia, amnesia
- Rare: ataxia, convulsions, syncope, speech disorders
- Not Known: serotonin syndrome.

Eye disorders:

- Rare: vision blurred, miosis, mydriasis

Ear and labyrinth disorders:

- Uncommon: tinnitus

Cardiac disorders:

- Uncommon: palpitations, tachycardia, arrhythmia.

Vascular disorders:

- Uncommon: hypertension, hot flush

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

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

Investigations:

- Uncommon: transaminases increased

Post marketing surveillance

very rare: abuse.

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 ($\geq 1/10000$ to $< 1/1000$) : allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
- Rare cases ($\geq 1/10000$ 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 drug withdrawal syndrome, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

Paracetamol

- Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
- There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.
- Very rare cases of serious skin reactions have been reported.

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 HPRC pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Tramadol/Paracetamol effervescent is a fixed combination of active substances. 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.

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.

Symptoms of overdose from paracetamol:

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Liver damage is possible in adults who have taken 7.5-10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Emergency treatment:

- Transfer immediately to a specialised unit.
- Maintain respiratory and circulatory functions
- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.
- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.
- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
- supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol hydrochloride is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramadol/Paracetamol effervescent 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.

Serotonin syndrome has also been reported.

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 gastro-intestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects. Tramadol/Paracetamol effervescent 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 hydrochloride 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 hydrochloride/paracetamol (37.5 mg/325 mg) effervescent tablet, mean peak plasma concentrations of 94.1 ng/ml for racemic tramadol and 4.0 mcg/ml for paracetamol are reached after 1.1 h (racemic tramadol) and 0.5 h (paracetamol), respectively. The mean terminal phase half-lives ($t_{1/2}$) are 5.7 h for racemic tramadol and 2.8 h for paracetamol.

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Tramadol/Paracetamol effervescent, 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/Paracetamol effervescent, 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 hydrochloride.

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

Distribution:

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

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

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

Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P 450 to an active intermediate (the N-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Elimination:

Tramadol and its metabolites are eliminated mainly by the kidneys. The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9% of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

5.3 Preclinical safety data

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

The combination tramadol hydrochloride/paracetamol has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol hydrochloride/paracetamol), i.e., 8.3 times the maximum therapeutic dose in man based on body surface. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe materno-toxic effect (10/87 and 25/217 mg/kg tramadol hydrochloride/paracetamol) did not result in toxic effects in the embryo or the foetus.

Results of standard mutagenicity tests did not reveal a potential genotoxic risk for tramadol hydrochloride in man.

Results of carcinogenicity tests do not suggest a potential risk of tramadol hydrochloride for man.

Animal studies with tramadol hydrochloride 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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous citric acid (E330)
Sodium citrate monobasic (E331)
Sodium hydrogen carbonate (E500)
Sodium carbonate anhydrous (E500)
Povidone K 25 (E1201)
Saccharin sodium (E954)
Acesulfame potassium (E950)
Polyethylene glycol 6000 (E1521)
Orange flavour (contains maize maltodextrin, sugar, soy-lecithins (E322), silicon dioxide (E551), natural flavouring substances)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Surlyn strip (Paper / PE / 15 µm Aluminium / Surlyn) packs: containing: 10, 20, 30, 50, 60 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Limited,
Euro House, Euro Business Park,
Cork, T45 K857,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/244/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd December 2021

10 DATE OF REVISION OF THE TEXT