4. CLINICAL PARTICULARS

4.2 Posology and method of administration

Posology

Adults and Adolescents (12 years and older) (Adults and young people aged 15 and older)

The use of <Tradename> 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 individually adjusted according to intensity of pain and response of the patient.

An initial dose of two tablets of <Tradename> (equivalent to 75 mg tramadol hydrochloride and 650 mg paracetamol) is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day. The dosing interval should not be less than six hours.

<Tradename> 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 <Tradename> 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.

Children

The effective and safe use of <Tradename> has not been established in children below the age of 12 years (aged under 15 years). Treatment is therefore not recommended in this population.

Elderly patients

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

Renal insufficiency

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

Hepatic insufficiency

In patients with severe hepatic impairment <Tradename> should not be used (see section

4.3). In moderate cases prolongation of the dosage interval should be carefully considered (see section 4.4).

Method of administration

Oral use.

<Tradename> 37.5 mg/325 mg film-coated tablets

Tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

<Tradename> 37.5 mg/325 mg effervescent tablets

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

4.3 Contraindications

- Hypersensitivity to tramadol hydrochloride, paracetamol, sunset yellow[1] or to any of the excipients (see section 6.1) of the medicinal product,
- acute intoxication with alcohol, hypnotic medicinal products, centrally-acting analgesics, opioids or psychotropic medicinal products,
- <Tradename> 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 (15 years) and older the maximum dose of 8 tablets of <Tradename> 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), <Tradename> is not recommended.
- In patients with severe hepatic impairment, <Tradename> 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, <Tradename> is not recommended.

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* The local deviations are highlighted in underlined letters in brackets.

- 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 <Tradename> 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).

Precautions for use

<Tradename> 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 overdose may cause hepatic toxicity in some patients.

At therapeutic doses, tramadol hydrochloride has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported (see section 4.8).

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur (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.

<Tradename> 37.5 mg/325 mg effervescent tablets

The colorant Sunset yellow E110 may cause allergic reactions.
This medicinal product contains 7.8 mmol (or 179.4 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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

(consciousness disorder), even coma.

- Selective-A MAO inhibitors
  Extrapolation from non-selective MAO inhibitors
  Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, (consciousness disorder), even coma.

- Selective-B MAO inhibitors
  Central excitation symptoms evocative of a serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, (consciousness disorder), even coma.

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

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:

- In isolated cases there have been reports of Serotonin Syndrome in a temporal connection with the therapeutic use of tramadol hydrochloride in combination with other serotoninergic medicines such as selective serotonin re-uptake inhibitors (SSRIs) and triptans. Signs of Serotonin Syndrome may be for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.

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

- Other central nervous system depressants, such as other opioid derivatives (including antitussive medicinal products and substitutive treatments), barbiturates, benzodiazepines, 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.

- As medically appropriate, periodic evaluation of prothrombin time should be performed when <Tradename> and warfarin like compounds are administered concurrently due to reports of increased INR.

- Other active substances 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 hydrochloride with these medicinal products 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 hydrochloride in patients with postoperative pain.

4.6 Pregnancy and lactation

Pregnancy

Since <Tradename> is a fixed combination of active substances including tramadol hydrochloride, it should not be used during pregnancy.

Data regarding paracetamol:

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosages.

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.

Lactation

Since <Tradename> is a fixed combination of active substances including tramadol hydrochloride, it should not be ingested 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:

Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of the dose given to the mother. Tramadol hydrochloride should not be ingested during breast feeding.

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. (Patients taking tramadol should not drive or operate machines).

4.8 Undesirable effects

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

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

Psychiatric disorders
- Common (≥ 1/100 to < 1/10): confusion, mood altered, anxiety, nervousness, euphoria, sleep disorders
- Uncommon (≥ 1/1000 to < 1/100): depression, hallucinations, nightmares, amnesia
- Rare (≥ 1/10000 to < 1/1000): drug dependence

Post marketing surveillance:
- very rare (< 1/10000): abuse

Nervous system disorders
- Very common (≥ 1/10): somnolence, dizziness
- Common (≥ 1/100 to < 1/10): headache, trembling
- Uncommon (≥ 1/1000 to < 1/100): muscular contractions involuntary, paraesthesia
- Rare (≥ 1/10000 to < 1/1000): convulsions, ataxia

Eye disorders
- Rare (≥ 1/10000 to < 1/1000): blurred vision

Ear and labyrinth disorders

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

Cardiac disorders
- Uncommon (≥ 1/1000 to < 1/100): arrhythmia, tachycardia, palpitations

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

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

Skin and subcutaneous tissue disorders
- Common (≥ 1/100 to < 1/10): sweating, pruritus
- Uncommon (≥ 1/1000 to < 1/100): dermal reactions (e.g. rash, urticaria)

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

General disorders and administration site conditions
- Uncommon (≥ 1/1000 to < 1/100): chills, chest pain (Whole body:- Rare: shivering, hot flashes, thoracic pain)

Investigations
Uncommon (≥ 1/1000 to < 1/100): transaminases increased (elevated aminotransferase activity)

Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol hydrochloride or paracetamol cannot be excluded:

Tramadol hydrochloride:

- Postural hypotension, bradycardia, collapse.
- Post-marketing surveillance of tramadol hydrochloride 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.

* The local deviations are highlighted in underlined letters in brackets.

- Psychic side-effects may occur following administration of tramadol hydrochloride which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood, (usually elation 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.

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.

4.9 Overdose

<Tradename> 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 substances.

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 overdose 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) (serum hepatic enzyme activity) 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 (intravenous) diazepam.
- Tramadol hydrochloride is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with <Tradename> 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.