Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramapine 200 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release tablet contains 200 mg tramadol hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Tramapine 200 mg prolonged release tablets are off white, capsule shaped tablets, 17.1 mm long.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

Posology

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

Unless otherwise prescribed, Tramapine prolonged-release tablets should be given as follows:

Adults and adolescents older than 12 years:

The usual initial dose is 50 - 100 mg tramadol hydrochloride twice daily, morning and evening.

If pain relief is insufficient, the dose may be titrated upwards to 150 mg or 200 mg tramadol hydrochloride twice daily.

For doses not practicable with this strength, other strengths of this medicinal product are available.

Tramapine prolonged-release tablets should be swallowed completely, without breaking or chewing, independent of meals, with sufficient liquid.

Daily doses of 400 mg of active substance should not be exceeded, except in special clinical circumstances.

Under no circumstances should Tramapine be used for longer than absolutely necessary.

If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether, and to what extent, further treatment is necessary.

Paediatric population

Tramapine is not suitable for children under the age of 12 years.

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 insufficiency / dialysis and hepatic impairment
In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage interval should be carefully considered according to the patient's requirements.

Method of administration

Oral use

4.3 Contraindications

Tramapine prolonged-release tablets are contraindicated:

- in hypersensitivity to the active substance, or to any of the excipients listed in section 6.1,
- in acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal products.
- in patients receiving MAO inhibitors, or who have taken them within the last 14 days (see section 4.5).
- in patients with epilepsy not adequately controlled by treatment
- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Tramapine may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure.
In patients sensitive to opiates the product should only be used with caution.
Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

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 daily dose limit (400 mg).
In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold. (see section 4.5). Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

Tramadol has a low dependence potential. On long-term use tolerance, psychiatric and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment with Tramapine should only be carried out for short periods under strict medical supervision.

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

4.5 Interaction with other medicinal products and other forms of interaction

Tramapine should not be combined with MAO inhibitors (see section 4.3). In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with Tramapine as with MAO inhibitors cannot be ruled out during treatment with Tramapine.

Concomitant administration of Tramapine with other centrally depressant medicinal products, including alcohol, may potentiate the CNS effects (See section 4.8).
The results of pharmacokinetic studies have so far, shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of the action.

The combination of mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, anti-psychotics and other 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 and mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) and probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied (See section 4.8).

In a limited number of studies the pre-or postoperative application of the antiemetic 5-HT_3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality.
Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore Tramapine should not be used in pregnant women.
Tramadol – administered before or during birth – does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

During lactation about 0.1% of the maternal dose administered is secreted into the milk. Tramapine is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions Tramapine may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with other psychotropic substances, and alcohol.

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10 % of patients.

The frequencies are defined as follows:
Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1,000, <1/100
Rare: ≥1/10,000, <1/1,000
Very rare (<1/10,000),
Not known (cannot be estimated from the available data).

Cardiovascular disorders:
Uncommon: effects on cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially on intravenous administration and in patients who are physically stressed.
Rare: bradycardia, increase in blood pressure.

Metabolism and nutrition disorders
Not known: hypoglycaemia

Nervous system disorders:
Very common: dizziness
Common: headache, somnolence
Rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.
Not known: speech disorders

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.
Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with drugs which can lower the seizure threshold or themselves induce cerebral convulsions (see section 4.4 and section 4.5).

Psychiatric disorders:
Rare: hallucinations, confusion, anxiety, sleep disturbances and nightmares. Psychiatric adverse reactions may occur following administration of Tramapine which vary individually in intensity and nature (depending on personality and duration of treatment). 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).
Dependence may occur.

Eye disorders:
Rare: blurred vision.
Not known: mydriasis

Respiratory disorders:
Rare: dyspnoea
Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders:

Very common: nausea
Common: vomiting, constipation, dry mouth.
Uncommon: Retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea.

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

Musculoskeletal disorders:
Rare: motorial weakness.

Hepato-biliary disorders:
In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.
Renal and urinary system disorders:
Rare: micturition disorders (difficulty in passing urine, dysuria and urinary retention).

General disorders:
Common: fatigue.
Rare: Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis;
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 with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Symptoms
In tramadol intoxication, in principle, the same symptoms occur as for all other central acting analgesics (opioids). In particular, these include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment
The general emergency measures apply. Keep open the respiratory tract (aspiration), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such case diazepam should be given intravenously.

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or prolonged-release formulations.

Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore treatment of acute intoxication with Tramapine with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids
ATC code: N 02 AX 02:

Tramadol is a centrally acting opioid analgesic.
It is a non-selective, partial agonist of μ-, δ- and κ-opioid receptors with a higher affinity for μ-receptors. Other mechanisms contributing to the analgesic effect are the inhibition of the neural noradrenaline reuptake, and an enhancement of serotonin release.

Tramadol has an antitussive action.
In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect.
Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight.
The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

5.2 Pharmacokinetic properties

More than 90% of tramadol is absorbed after oral administration.
The mean absolute bioavailability is approximately 70%, irrespective of concomitant intake of food.

The difference between absorbed and non-metabolised available tramadol is probably due to low first–pass effect. The first-pass effect after oral administration is a maximum of 30%.

Tramadol has a high tissue affinity ($V_{d,\beta}$ = 203 ± 40 L). Protein binding is about 20%.

After administration of Tramapine 100 mg tablets the peak plasma concentration C_{max} 141 ± 40 ng/ml is reached after 4.9 hours. After administration of Tramapine 200 mg tablets a C_{max} 260 ± 62 ng/ml is reached after 4.8 hours.

Tramadol passes the blood-brain and placenta barrier. Very small amounts of the substance and its O-desmethyl derivative are found in the breast – milk (0.1% and 0.02% respectively of the applied dose).

Elimination of half-life t½β is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

In humans tramadol is mainly metabolized by means of N- and O- demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2-4. Its half life $t½_{\beta}$ (6 healthy volunteers) is 7.9 h (range 5.4-9.6 h) and is approximately that of tramadol.
The inhibition of one or both cytochrome p450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite. Up to now, clinically relevant interactions have not been reported.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 ± 3.2 h and 16.9 ± 3 h, in an extreme case 19.5 h and 43.2 h, respectively.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100-300 ng/ml is usually effective.

5.3 Preclinical safety data

On repeated oral and parenteral administration of tramadol during 6 to 26 weeks in rats and dogs and oral administration for 12 months in dogs haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate (E341),
Hydroxypropylcellulose (E463),
Colloidal anhydrous silica (E551),
Magnesium stearate (E470b).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

PP / PE tablet container: 6 months after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Al / clear PVC blisters in carton boxes in packs of 10, 20, 30, 50, 60, 90, 100, 120, 180, and 500 tablets.
Al / opaque PVC child resistant blisters in carton boxes in packs of 10, 20, 30, 50, 60, 90, 100, 120, 180, and 500 tablets.
Polypropylene tablet container with polyethylene tamper evident closure containing 10, 20, 30, 50, 60, 90, 100, 120, 180, and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 281/100/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of authorisation: 4th May 2007
Date of last renewal: 27th October 2008

10 DATE OF REVISION OF THE TEXT

June 2014