Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramapine 50mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50mg of Tramadol hydrochloride.

Excipient: Also contains 103mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsules
Green and yellow gelatin capsules, printed ‘TRA 50’ on both cap and body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management (treatment and prevention) of severe pain.

4.2 Posology and method of administration

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. Treatment periods should be short and intermittent as dependence can occur with tramadol. The benefits of continued use should be reviewed in order to ensure that they outweigh the risks of dependence (see Warnings & Precautions for Use and Undesirable Effects Sections).

Adults and children over the age of 14 years:
Depending upon the severity of the pain, the initial dose is 50 to 100 mg tramadol, then 50 mg to 100 mg 4-6 hourly. If tramadol is used for the treatment of acute pain, it should be taken into account that the effect starts slightly later than that of other analgesics. For acute pain an initial dose of 100 mg is usually required. For pain associated with chronic conditions, an initial dose of 50 mg is recommended. A total daily dose of more than 400 mg is not usually required.

Geriatric 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 and hepatic impairment
In patients with renal and/or hepatic 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. Further guidance is below:
The usual initial dose may be used, however the interval between subsequent doses should be twice as long. In patients with both renal and hepatic impairment, the use of tramadol should be avoided.

Renal Dialysis
Tramapine is removed very slowly by haemodialysis or haemofiltration, therefore post dialysis administration to maintain analgesia is not usually necessary.

Children aged 1 year to 14 years
The dose is 1-2 mg/kg body weight at 4-6 hourly. There is no experience with children under the age of 1 year.

Route of administration: Oral.

4.3 Contraindications

- Hypersensitivity to tramadol or any of the excipients listed in section 6.1 or other opioids.
- Acute intoxication with alcohol, hypnotics, analgesics, opioids or other psychotropic drugs.
- Tramadol should not be administered to patients concomitantly with monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal (see section 4.5).
- Patients with epilepsy not adequately controlled by treatment.
- Use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Tramadol has the potential to cause physical dependence and withdrawal symptoms at therapeutic doses (see section 4.8 Undesirable Effects).
Tramapine 50 mg capsules should be used with particular caution in patients with head injury, a reduced level of consciousness of uncertain origin, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.

In patients sensitive to opiates the product should only be used with caution.

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 limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medication that affects the seizure threshold (see section 4.5 Interaction with other medicinal products and other forms of interaction*)*. Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Care should be taken when treating patients with severe respiratory depression or disorder of respiratory function, if concomitantly CNS depressant drugs are being administered or if the recommended dose is exceeded considerably, since the possibility of respiratory depression cannot be excluded in these situations.

Tolerance, psychic and physical dependence may develop, especially after long-term use. In patients with a tendency to drug abuse or dependence, treatment with tramadol should only be carried out for short periods under strict medical supervision.

Tramapine is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, it cannot suppress morphine withdrawal symptoms. For physical dependency, addiction and habituation: see section 4.8 Undesirable Effects.

In one study use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intraoperative recall. Until further information is available use of Tramapine with such anaesthesia should be avoided.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of tramadol with monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal is contra-indicated (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 MAO inhibitors cannot be ruled out during treatment with Tramapine.

Concomitant administration of tramadol with other centrally acting drugs including alcohol may potentiate CNS depressant 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 action. Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics 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.

There have been isolated spontaneous reports of epileptiform convulsions which in most instances occurred after

intravenous administration of a high single dose of tramadol or during concomitant use with antipsychotics known to induce convulsions.

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.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. The elimination half-life of tramadol may be slightly prolonged by some 1-2 hours. Under normal circumstances this should be insufficient to have clinical relevance. However, because of inter-individual variation, it is recommended that care should be taken if prolonged co-administration with agents such as cimetidine is needed.

Simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to the extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

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 (see section 4.8).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is inadequate evidence available on safety of tramadol in human pregnancy, but it has been in wide use for many years without apparent ill consequences. Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore tramadol should not be used in pregnant women. Tramadol may be used during delivery.

Breastfeeding
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.

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 and other psychotropic substances, particularly alcohol.

4.8 Undesirable effects

a) Summary of the safety profile
The most commonly reported adverse drug reactions are nausea and dizziness, both occurring in more than 10% of patients.

b) List of adverse effects
Very common (>1/10), Common (>1/100, <1/10), Uncommon (> 1/1000, <1/100), Rare (>1/10,000, <1/1000), Very rare (<1/10,000) Not Known (cannot be estimated from the available data).

Immune system disorders:
Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.

Metabolism and nutrition disorders
Not known: Hypoglycaemia, changes in appetite.

Psychiatric disorders:
Rare: hallucinations, confusion, sleep disturbance, delirium anxiety and nightmares. Psychiatric 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 moods (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders). Drug dependence may occur.

Nervous system disorders:
Very common: Dizziness.

Common: Headache, somnolence.

Rare: Paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.

Unknown: Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with drugs which can lower the seizure threshold (see sections 4.4 and 4.5).

Eye disorders:
Rare: Blurred vision.

Cardiac disorders:
Uncommon: cardiovascular regulation (palpitation, tachycardia). These adverse effects may occur especially on intravenous administration and in patients who are physically stressed.

Rare: Bradycardia, increase in blood pressure.

Vascular disorder:
Uncommon: cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse effects may occur especially on intravenous administration and in patients who are physically stressed.

Respiratory, thoracic and mediastinal disorders:
Rare: respiratory depression, dyspnoea

Unknown: Worsening of asthma has been reported, although a causal relationship has not been established.

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see Section 4.5), respiratory depression may occur.

Gastrointestinal disorders:
Very common: Nausea

Common: Constipation, dry mouth, vomiting.

Uncommon: Retching, gastrointestinal discomfort (feeling of pressure in the stomach, abdominal distension), diarrhoea.

Hepatobiliary disorders:
Unknown: In isolated cases, increases in liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders:
Common: Hyperhidrosis.

Uncommon: Dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders:
Rare: Motorial weakness.

Urinary system disorders:
Rare: Micturition disorders (dysuria and urinary retention).

General disorders and administration site conditions:
Common: Fatigue.

c) Description of selected adverse events

Physical Dependence:
Dependence, abuse, addiction and withdrawl reactions may occur. The majority of withdrawl reaction symptoms are similar to those occurring during opiate withdrawl. Typical withdrawl reactions include 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, paraesthesia, tinnitus and unusual CNS symptoms.

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

4.9 Overdose

Symptoms
The symptoms of overdose are typical for opioid-analgesics and include miosis, vomiting, cardiovascular collapse, sedation and consciousness disorders up to a coma, convulsions and respiratory depression up to respiratory arrest.

Treatment
Supportive measures such as maintaining respiratory and cardiovascular functions should be instituted; naloxone should be used to reverse respiratory depression; convulsions can be controlled with diazepam. 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 formulation. As tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration, treatment of acute intoxication with Tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Nervous system
ATC code: NO2 AX02.

Tramadol is a centrally acting analgesic, effective for moderate to severe acute and chronic pains. Tramadol consists of two enantiomers.

The (+)-isomer is predominantly active as an opiate with a higher affinity for the (mu) μ-opiate receptor (20 times higher affinity than the (-) isomer).

The (+) desmethyl metabolite will certainly contribute to its action as an opiate as well. The metabolite has a six times stronger affinity for the μ-receptor in vivo than tramadol. *In vivo* this affinity is 170 times stronger. The (-) isomer acts as an inhibitor of the re-uptake of noradrenaline and potentiates the analgesic action of the (+) isomer. The contribution of the stimulation of the serotonin release is considered low.

Tramadol has an analgesic and antitussive effect. Unlike morphine respiratory suppression is hardly observed at therapeutic doses. The influence on gastro-intestinal motility and on the cardiovascular system is low at these doses.

Paediatric population
Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2).

5.2 Pharmacokinetic properties

Tramadol is absorbed rapidly and completely after oral administration. The absolute biological availability is 60-95%, (on average 72%). Maximum serum concentrations are reached after approx. 1 hour.

Plasma protein binding amounts to 20%. Tramadol passes the blood-brain barrier and the placenta. The excretion of tramadol or its metabolites in human breast milk is small (± 0.1%). Tramadol is especially metabolized by demethylation followed by glucoronidisation of the 0-desmethyl-metabolite. Only 0-desmethyl-tramadol is pharmacologically active. Tramadol and its metabolites are almost completely excreted renally, of which approximately 10% as unchanged pharmacon.
The half life of the terminal elimination phase of both tramadol as its metabolites is approximately 6 hours, both in young volunteers as in elderly patients. Since tramadol is eliminated both metabolically and renally, the half life of the terminal elimination phase may be prolonged in impaired hepatic and renal function. In those cases the half life of the terminal elimination phase is twice as long. In patients with both renal and hepatic impairment, the use of tramadol should be avoided.

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

5.3 Preclinical safety data

No particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose (E460)
Povidone K30
Lactose Monohydrate
Magnesium Stearate
Sodium Starch Glycolate

Capsule shell components
Titanium dioxide (E171)
Gelatin
Indigotine (E132)
Erythrosin (E127)
Yellow Iron Oxide (E172)

Capsule Ink
Shellac
Propylene glycol
Ammonia solution concentrated
Potassium hydroxide
Black Iron Oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC/PVDC blister packs in a carton box.

Pack sizes: 30, 50, 100, 250 and 500 capsules.

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 Ltd., trading as
Pinewood Healthcare
Ballymacarbry
Clonmel
Co.Tipperary

8 MARKETING AUTHORISATION NUMBER

PA0281/100/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2001

Date of last renewal: 13 July 2006

10 DATE OF REVISION OF THE TEXT

July 2018