Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramake 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Tramadol hydrochloride 50 mg.

Excipient(s) with known effect: contains 50mg of lactose monohydrate per tablet.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White uncoated tablets marked 'T50' on one side and the other side is plain and unmarked.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tramake 50mg Tablets are indicated in adults and adolescents aged 12 years and over for the treatment and prevention of severe pain.Tramadol has been found to be of benefit in both acute and chronicpain states.

4.2 Posology and method of administration

Posology
Tramake 50mg Tablets should not be used in children aged 0 to 12 years.
Older children (aged 12 years and over) and adults: 50-100mg every 4-6 hours. 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.

For acute pain a starting dose of 100mg is most often required.Chronic conditions usually respond to 50mg starting dose.

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 sections 4.4 and 4.8).

No more than 400mg orally is usually necessary for pain management in any 24 hour period.

Elderly patients
A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepaticor renal insufficiency. I n 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 thepatient's requirements.

As tramadol is only removed very slowly by haemodialysis or by haemo filtration, post- dialysis administration to maintain analgesiais not usually necessary.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Tramadol should be avoided in patients with acute intoxication of alcohol, centrally actinganalgesics, opioids, hypnotics or psychotropic drugs. Tramadol is contraindicated in patients who have received monoamineoxidase inhibitors (MAOIs) in the last two weeks and in patients receiving buprenorphine, nalbuphine or pentazocine (see section 4.5).Tramadol is also contraindicated in patients whose epilepsy is not controlled by an adequate treatment.

4.4 Special warnings and precautions for use

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%

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Tramake 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 Tramake concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

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).

Caution should be exercised when administering tramadol to patients with pre-existing respiratory depression.

Tolerance, psychic and physical dependence may develop, especially after long-term use. In patients with a tendency to drug abuse or dependence, treatment with Tramake should only be carried out for short periods under strict medical supervision. In rare cases at therapeutic doses, tramadol has the potential to cause withdrawal symptoms (see section 4.8).

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

It is not a suitable substitute for other opioids in cases of withdrawal.

Tramadol may cause drowsiness, blurred vision and dizziness which are potentiated by alcohol and other centrally acting agents. Patients should be warned to avoid alcohol and not to drive or operate heavy machinery until the effect on mental activity is established.

Care should be taken when administering tramadol to patients with head injury, raised intracranial pressure or shock.

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 (400mg). Convulsions have been reported in patients susceptible to seizures or taking other medications that lower the seizure threshold, see Section 4.5. Therefore, patients with epilepsy, those susceptible to seizures or those patients taking other medications that lower the seizure threshold should only be treated with tramadol if there are compelling circumstances.

Renal impairment may cause the elimination of tramadol to be prolonged and elimination may also be prolonged in hepatic dysfunction (see section 4.2).

Tramadol is unsuitable for use as an intraoperative analgesic as increased awareness has been experienced.

This medicinal product contains lactose monohydrate, therefore patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

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.

4.5 Interaction with other medicinal products and other forms of interactions

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline (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-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3 and below), 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.

MAOIs: In case of recent treatment with MAOIs, treatment with tramadol should not start until two weeks after cessation of treatment with MAOIs.

Sedative medicines such as benzodiazepines or related drugs: 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 central nervous system (CNS) depressant effects. The dose and duration of concomitant use should be limited (see section 4.4).

CNS effects such as drowsiness may also be enhanced with concomitant use of alcohol.

Cimetidine, an enzyme inhibitor, retards breakdown of tramadol. This effect is however clinically insignificant so no alteration in dose is necessary.

The hepatic enzyme inducer carbamazepine promotes tramadol metabolism. The duration of action and analgesic effect may be reduced in patients receiving carbamazepine.

Mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine): The analgesic effect of tramadol which is a pure agonist may be reduced, and a withdrawal syndrome may occur (see section 4.3).

Other morphine derivatives (including antitussives, substitution treatments): Increased risk of respiratory depression, that may be fatal in case of overdosage.

Coumarin anticoagulants: There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR and so, care should be taken if treatment with tramadol is started in patients taking anticoagulants.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity. Animal studies with tramadol at very high doses revealed effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There are a limited amount of data from the use of tramadol in pregnant women. Chronic use of tramadol during pregnancy may lead to withdrawal symptoms in newborn infants. Therefore, Tramake is not recommended during pregnancy. Tramadol used at the end of pregnancy may induce respiratory depression in newborn infants.

Breast feeding

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 400mg, this corresponds to a mean amount of tramadol ingested by breastfed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breastfeeding should be discontinued during treatment with tramadol. Discontinuation of breastfeeding is generally not necessary following a single dose of tramadol.

4.7 Effects on ability to drive and use machines

Tramake may cause drowsiness, blurred vision and dizziness which are potentiated by alcohol and other centrally acting agents.Patients should be warned to avoid alcohol and not to drive or operate heavy machinery until the effect on mental activity is established.

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following frequency data:
Very common (≥1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from available data)

System Organ Class	**Frequency of adverse reactions**					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system						Blood

disorders						dyscrasias
Immune system disorders						Anaphylaxis
Metabolism and nutrition disorders				Changes in appetite		Hypoglycaemia
Psychiatric disorders				Euphoria, Nightmares, Confusion, Hallucinations, Delirium		Dysphoria, Dependence, Abuse, Withdrawal
Nervous system disorders	Dizziness	Sedation, Headache	Fainting	Paraesthesia, Convulsions		
Eye disorders				Blurred vision		
Cardiac disorders			Tachycardia	Bradycardia		
Vascular disorders			Orthostatic hypotension		Flushing	
Respiratory, thoracic and mediastinal disorders						Respiratory depression, Worsening of existing asthma, Dyspnoea, Wheezing, Bronchospasm
Gastrointestinal disorders	Nausea, Vomiting	Dry mouth, Constipation, Gastro-intestinal irritation				
Hepatobiliary disorders						An increase in liver enzymes
Skin and subcutaneous tissue disorders		Diaphoresis	Pruritis, Urticaria			Quincke's oedema, Skin rash
Renal and urinary disorders				Difficulty in passing urine, Urinary retention		
General disorders and administration site conditions		Tiredness				
Investigations				Increase in blood pressure		

Respiratory depression has been reported. If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly, respiratory depression may occur.

Confusion and/or hallucinations and dysphoria have been rarely reported. Convulsions, essentially in cases of treatment with high doses, or in cases of concomitant treatment with drugs that lower the epileptic threshold (see sections 4.4 and 4.5) have been reported.

Physical Dependence: Dependence, abuse and withdrawal reactions have been reported. Agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal symptoms may occur as part of the withdrawal reaction, which is similar to those occurring during opiate withdrawal.

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
Website: www.hpra.ie

4.9 Overdose

Like other opioids tramadol can cause miosis, constipation, respiratory depression, convulsions, coma and cardiovascular collapse. These effects can be reversed using the opioid antagonist naloxone; fits may be controlled by diazepam. Supportive measures such as maintaining cardiovascular and pulmonary function should be initiated. In cases of acute tramadol intoxication, treatment with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics – other opioids, ATC code N02AX02

Tramadol is a synthetic opioid analgesic. It has agonist activity at opioid receptors and also produces analgesia through inhibition of serotonin and noradrenaline uptake. It has been found to be effective in the treatment and prevention of pain of varying aetiologies with analgesia lasting for 3-6 hours.

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 2mg/kg or multiple doses of up to 8mg/kg per day (to a maximum of 400mg 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

Bioavailability following single dose administration is around 68% increasing to approximately 90% after multiple oral dosing. Plasma concentrations are detectable from 15 minutes with peak levels occurring 90-120 minutes post dose. Tramadol is mainly metabolised in the liver. 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.

Elimination is essentially via the kidney though some tramadol is excreted in the faeces. The elimination half-life is 5-6 hours.

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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25º C.

6.5 Nature and contents of container

PVC (250 micrometres) /Aluminium (20 micrometres) blisters.

Pack sizes: 1, 2, 3, 4, 6, 9, 10, 12, 20, 21, 30, 60, 84, 90, 100, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Galen Pharma Ireland Limited
Finnabair Industrial Estate
Dundalk
Louth
A91P9KD
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22680/003/001

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Date of last renewal: 04 February 2010

10 DATE OF REVISION OF THE TEXT

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