Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramake Insts 100mg Sachets
Powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 100mg tramadol hydrochloride.
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.
White fine free flowing powder with a lemon odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment and prevention of severe pain. Tramadol has been found to be of benefit in both acute and chronic pain states.

4.2 Posology and method of adminstration

For oral administration after reconstitution with water. Add the contents of each sachet to half a glass of water (150ml) to produce a clear solution with a lemon odour and flavour. Stir to dissolve and drink immediately.

Children (0-12 years): Not recommended.

Older children (Aged 12 years and over) and Adults: 50-100mg every 4-6 hours.

Elderly: Adult dose is usually suitable.

Renal impairment

Creatinine clearance < 30 ml/min: increase interval between doses to 12 hours.

Creatinine clearance < 10 ml/min: not recommended.

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

Hepatic impairment

Severe dysfunction: Increase interval between doses to 12 hours.
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.

4.3 Contraindications

As with any other medicament Tramake should not be given to patients who have previously demonstrated a hypersensitivity to any of the ingredients. It should be avoided in patients with acute intoxication of alcohol, centrally acting analgesics, opioids, hypnotics or psychotropic drugs. Tramadol is contra-indicated in patients who have received monoamine oxidase inhibitors (MAOIs) in the last two weeks and in patients receiving buprenorphine, nalbuphine or pentazocine (see Section 4.5). Tramadol is also contra-indicated in patients whose epilepsy is not controlled by an adequate treatment.

Tramake Insts 100mg Sachets should be avoided in patients who have the metabolic disorder phenylketonuria. This product contains aspartame which is a source of phenylalanine.

4.4 Special warnings and precautions for use

Tramadol has the potential to cause physical dependence at therapeutic doses. As tramadol has opioid agonist activity there is potential for abuse and dependence to develop. Its reported physical dependence potential is however very low.

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, especially selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), antipsychotics, centrally acting analgesics or local anaesthetics (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. Where the creatinine clearance is below 30 ml/min the time between doses should be increased to 12 hours. Tramadol is not recommended for administration to patients with creatinine clearance less than 10 ml/min.

Elimination may also be prolonged in hepatic dysfunction. For severe hepatic dysfunction the time between doses should be increased to 12 hours.

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

Although respiratory depression is reported rarely the possibility of it developing cannot be ignored. Caution should be exercised when administering tramadol to patients with pre-existing respiratory depression or with concomitant administration of CNS drugs.

Each Tramake Insts 100mg Sachet contains 335.4mg of sodium. This should be taken into account when prescribing for patients on a sodium restricted diet.

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system effects such as drowsiness may be enhanced with concomitant use of centrally acting agents and 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.

Tramadol can induce convulsions and increase the potential for SSRIs, TCAs, antipsychotics and other threshold lowering drugs to cause convulsions (see Section 4.4).

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).

MAOIs: A serotoninergic syndrome is likely to occur: diarrhoea, tachycardia, sweating, tremor, confusion, coma. In case of recent treatment with MAOIs, treatment with tramadol should not start until two weeks after cessation of treatment with MAOIs.

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

Serotonergic drugs: Co-administration with serotonergic drugs (e.g. SSRIs, triptans) may lead to an increase of serotonin associated effects which can include serotonin syndrome.

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 Pregnancy and lactation

Animal studies with tramadol at very high doses revealed effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. However this drug should not be used in pregnancy as no specific studies concerning its effect on the human foetus are available.

Approximately 0.1% of an oral dose of tramadol is excreted in breast milk. Although the concentration is low, tramadol is not recommended during breast feeding.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Most frequently reported adverse events are nausea, sedation, dizziness, vomiting, headache, diaphoresis, skin rash and dry mouth. Tramadol may also cause constipation, pruritis, urticaria, dyspnoea, wheezing, bronchospasm and worsening of existing asthma, gastro-intestinal irritation, tachycardia, bradycardia, orthostatic hypotension, flushing, fainting and blood dyscrasias, blurred vision, difficulty in passing urine, urinary retention, tiredness, euphoria, increase in blood pressure, Quincke’s oedema, nightmares, changes in appetite, paraesthesia, an increase in liver enzymes and anaphylaxis.

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.

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

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.

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

5.3 Preclinical safety data

Not Applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate
Tartaric acid
Citric acid anhydrous
Sodium carbonate anhydrous
Aspartame (E951)
Lemon flavour (17.41.0212)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf Life

24 months.

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

Paper/Polymer-laminated aluminium sachets.

Pack sizes: 1, 2, 4, 6, 8, 10, 18, 20, 24, 30, 42, 56, 60, 84, 90, 100, 112, 168, 224, 250, 300 and 500 sachets.

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

Galen Limited
Seagoe Industrial Estate
Craigavon
BT63 5UA
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 185/35/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 November 1998

Date of last renewal: 13 November 2003

10 DATE OF REVISION OF THE TEXT

October 2005