Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramadol Hydrochloride 50 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Tramadol hydrochloride 50 mg (equivalent to Tramadol base 43.9 mg).

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Capsule, hard.
Opaque size No. 4 hard gelatine capsules containing a white odourless powder. “S12” may be embossed on either the yellow body or the green cap end of the capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tramadol capsules are indicated for the management of severe pain.

4.2 Posology and method of adminstration

Oral Use.

Depending upon the severity of the pain, the initial dose is 50mg or 100mg followed by 50 or 100mg not more frequently than 4 hourly. For acute pain an initial dose of 100mg is usually necessary. For pain associated with chronic conditions an initial dose of 50mg is advised. Treatment periods should usually be short, limited and intermittent as dependence can occur with tramadol. Treatment should be given only where there exists a medical need, and benefits of continued use should be reviewed in order to ensure that they outweigh the risks of dependence (see Special Warnings and Precautions for Use, and Undesirable Effects section).

A total oral daily dose of more than 400mg is not usually required.

Dosage in the elderly
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.

Dosage in renal impairment
The elimination of tramadol and its principal metabolite may be prolonged. The usual initial dosage should be used. For patients with creatinine clearance <30 ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance <10 ml/min).

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

Hepatic impairment
The elimination of tramadol and its principal metabolite may be prolonged. The usual initial dosage should be used but in severe hepatic impairment the dosage interval should be increased to 12 hours.

Dosage in children
Children under 14 years: Not recommended.

4.3 Contraindications

Tramadol should not be administered to patients who have previously demonstrated hypersensitivity to it or in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. In common with other opioid analgesics it should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

4.4 Special warnings and special precautions for use

Tramadol has the potential to cause physical dependence at therapeutic doses and cases of abuse and dependence have occurred.

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

Tramadol may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

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 limit (400mg). In addition, tramadol may increase the seizure risk in patients taking other medication that affects the seizure threshold (see Interactions).

Tramadol should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function, biliary tract disorders and in patients prone to convulsive disorders or in shock.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered or if the recommended dosage is significantly exceeded as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

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 tramadol during light planes of general anaesthesia should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of tramadol with other centrally acting drugs including alcohol may potentiate CNS depressant effects.

Tramadol can induce convulsions and increase the potential for both selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to an extent that a

decrease in analgesic effectiveness and a shorter duration of action may occur. There is a theoretical possibility that tramadol could interact with lithium, and 5HT and noradrenaline potentiating anti-depressants due to their respective mechanisms of action. There have been no reports of this potential interaction.

4.6 Pregnancy and lactation

There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore tramadol should not be used in pregnant women.

Animal studies (rat and rabbit, exposure to tramadol up to 7 times that expected in man) have revealed minimal embryotoxicity (delayed ossification) and have not revealed teratogenic effects. Fertility, reproductive performance and development of offspring were unaffected.

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

4.7 Effects on ability to drive and use machines

See Special Warnings and Precautions for Use.

4.8 Undesirable effects

Gastrointestinal system: Nausea, vomiting, constipation and occasionally dry mouth.

Central nervous system and psychiatric: Tiredness, fatigue, drowsiness, somnolence, dizziness, headache, confusion, hallucinations and infrequently, respiratory depression. Epileptiform convulsions, which in most instances followed intravenous use, dependence and dysphoria have been rarely reported.

Other adverse events: Dyspnoea, wheezing, bronchospasm, worsening of existing asthma, diaphoresis and pruritus has been reported. Skin rashes, tachycardia, orthostatic hypotension, increase in blood pressure, bradycardia, flushing, syncope, anaphylaxis and allergic hypersensitivity type reactions have been rarely reported. Cases of blood dyscrasias have been rarely observed during treatment with tramadol, but causality has not been established.

Physical dependence: Dependence, abuse and withdrawal reactions have been reported. Agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms may occur as part of a withdrawal reaction which is similar to that occurring during opiate withdrawal. (See Posology & Administration, and Special Warnings.)

4.9 Overdose

Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression.

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 diazepam.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tramadol is a centrally acting analgesic. It is a non selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

5.2 Pharmacokinetic properties

The half life of the terminal elimination phase (t½,β) was approximately 5 hours in young volunteers. Tramadol pharmacokinetics show little age-dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years the t½,β was 7 hours following oral administration.

Since tramadol is eliminated both metabolically and renally, the terminal half-life t½,β may be prolonged in impaired hepatic or renal function. However, the increase in the t½,β values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis and t½,β/tramadol was 13.3 hours; in patients with renal insufficiency (creatinine clearance ≤ 5ml/min) it was 10.8 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Magnesium stearate
Silica colloidal anhydrous
Gelatin
Quinoline yellow (E104)
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Indigo carmine (E132)
Opacode S-1-8100HV (Black 1007) containing:
(IMS 740P, shellac, black iron oxide (E172), 2-Ethoxyethanol, soya lecithin, dimeticone, purified water).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store in the original package.

Do not store above 30°C.

6.5 Nature and contents of container

White opaque PVC (200µ)/A1 foil (20µ) blister pack containing 10 capsules. Pack size 100 capsules.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1046/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 3rd April 1998

Date of Last Renewal: 3rd April 2003

10 DATE OF REVISION OF THE TEXT

March 2004