Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zytram SR 75mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing tramadol hydrochloride 75mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablets.

Pale grey film coated tablets marked "TBD" and "75".

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the management (treatment and prevention) of severe pain.

4.2 Posology and method of adminstration

ZYTRAM SR tablets should be taken at 12-hourly intervals and must be swallowed whole and not chewed.

Treatment periods should usually 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 section 4.4 and 4.8).

As with all analgesic drugs, the dose of tramadol should be adjusted according to the severity of the pain and the clinical response of the individual patient. The correct dosage for any individual patient is that which controls the pain with no or tolerable side effects for a full 12 hours. Patients transferring from immediate release tramadol preparations should have their total daily dose calculated, and start on the equivalent dose in the ZYTRAM SR range.

Thereafter, it may be necessary in some patients to increase the dosage in line with individual analgesic requirements (see section 5.2 for further information). It is recommended that patients are slowly titrated to higher doses to minimise transient side effects.

The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported. (See Section 4.4 Special Warnings and Precautions for Use). A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

Adults and children over 12 years:
The usual initial dose is one 75 mg tablet twice daily. If pain relief is not achieved, the dosage should be titrated upwards until pain relief is achieved.

Elderly and patients with renal or hepatic impairment:
The elimination half-life of tramadol may be prolonged in these patient populations. A starting dose of 75 mg twice daily is recommended. Dose titration upwards should be carefully monitored. Tramadol is not recommended for

patients with severe renal impairment (creatinine clearance < 10 ml/min).

Children under 12 years:
Not recommended.

4.3 Contraindications

Hypersensitivity to tramadol or any of the other constituents of the product; acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

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

4.4 Special warnings and precautions for use

Warnings
Tramadol has the potential to cause physical dependence at therapeutic dose (see Undesirable Effects).

At therapeutic doses withdrawal symptoms have been reported at a frequency of 1 in 8,000. Reports of dependence and abuse have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

In patients with a tendency to drug abuse or dependence, treatment should be for short periods and 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.

Precautions
Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400 mg). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold. (See Section 4.5 Interactions with other Medicaments and other forms of Interaction).

Tramadol should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function 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, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

In one study using a nitrous oxide/opioid (tramadol) anaesthetic technique (with only intermittent administration of enflurane ‘as required’) tramadol was reported to enhance intra-operative recall. Hence its use during potentially very light planes of general anaesthesia should be avoided.

Two recent studies of tramadol administration during anaesthesia comprising continuous administration of isoflurane did not show clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed, tramadol may be used intra-operatively in the same way as other analgesic agents are routinely used.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of tramadol with other centrally acting drugs, including alcohol, may potentiate CNS

depressant effects.

Simultaneous treatment with carbamazepine may shorten the analgesic effect as a result of a reduction in serum levels of tramadol and its active metabolite.

Co-administration with cimetidine is associated with a small prolongation of the half-life of tramadol, but this is not clinically relevant.

Tramadol may increase the potential for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions (see Section 4.4 Special Warnings and Special Precautions for Use and 5.2 Pharmacokinetic Properties). There is a theoretical possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.

4.6 Pregnancy and lactation

Pregnancy
Animal studies (rat and rabbit, exposure to tramadol up to 7 times that expected in man) have not revealed teratogenic effects and showed minimal embryotoxicity (delayed ossification).

Fertility, reproductive performance and development of offspring were unaffected.

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

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

4.7 Effects on ability to drive and use machines

Tramadol may cause drowsiness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

4.8 Undesirable effects

Gastrointestinal system:
Nausea, vomiting, and occasionally dry mouth. Both diarrhoea and constipation have been reported. In controlled trials the incidence of constipation is lower than that of comparator agents.

Central nervous system and psychiatric:
Tiredness, fatigue, drowsiness, somnolence, dizziness, headache, confusion, hallucinations and infrequently respiratory depression. Dysphoria and convulsions have been reported rarely.

Other adverse events:
Diaphoresis, urticaria, pruritus, dyspnoea, wheezing, bronchospasm and worsening of existing asthma have been reported. Skin rashes, tachycardia, orthostatic hypotension, increase in blood pressure, bradycardia, flushing, syncope and anaphylaxis 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. Typical opiate withdrawal reactions include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

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.

Emptying the gastric contents is useful to remove any unabsorbed drug, particularly when a prolonged release formulation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other opioids
ATC code: N02A X02

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 that may contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline and an enhancement of 5HT release.

5.2 Pharmacokinetic properties

Following oral administration of a single dose, tramadol is almost completely absorbed and the absolute bioavailability is approximately 70% following administration of a single dose. Tramadol is metabolised to O-desmethyltramadol, which has been shown to have analgesic activity in rodents. The elimination half life of tramadol is around 6 hours, although this is extended to around 12 hours following prolonged absorption from the ZYTRAM SR tablet.

Following administration of one ZYTRAM SR tablet 75 mg in the fasting state, a mean peak plasma concentration (C_{max}) of 80 $ng.ml^{-1}$ was attained. This was associated with a median t_{max} of 5 hours (range 3-7 hours). In the presence of food, the availability and prolonged release properties of ZYTRAM SR tablets were maintained, with no evidence of dose-dumping.

A single dose-proportionality study has confirmed a linear pharmacokinetic response (in relation to tramadol and O-desmethyltramadol) following administration of the 75 mg, 100 mg, 150 mg and 200 mg tablets. A steady state study has confirmed the dose adjusted bioequivalence of the 75 mg, 100 mg and 150 mg tablets administered twice-daily.

The pharmacokinetics of tramadol are non-linear. Faster-releasing formulations are associated with an accumulation of the drug substance, which is greater than would be anticipated from single dose data, a consequence of a saturated first-pass effect. The controlled delivery of tramadol from the range of ZYTRAM SR tablets minimises the non-linearity associated with faster-releasing preparations and consequently, single dose and steady state studies have demonstrated that, when compared with immediate release preparations, the mean availability of tramadol from the ZYTRAM SR tablet 75 mg was approximately 82%. On this basis it is recommended that patients receiving immediate release tramadol should be transferred initially to the nearest daily dose of ZYTRAM SR tablets. It may be necessary to titrate the dose thereafter. The more predictable plasma concentrations may lead to a more manageable dose titration process.

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

Hydrogenated Vegetable Oil
Talc
Magnesium Stearate
Lactose
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 4000
Iron oxide (E172)
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

1. PVC blisters with aluminium backing foil (containing 2, 7, 14, 28 or 56 tablets).

2. Polypropylene containers with polyethylene lids (containing 2, 7, 14, 28 or 56 tablets).

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 913/21/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st September 2000
Date of last renewal: 24th May 2004

10 DATE OF REVISION OF THE TEXT

January 2005