Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xymel 200 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 200 mg Tramadol hydrochloride.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release film coated tablets
Yellow, oblong, scored, film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management (treatment and prevention) of severe pain.

4.2 Posology and method of administration

As with all analgesic drugs, the dose of tramadol should be adjusted according to the severity of pain and the clinical response of the individual patient.

Adults and adolescents (over 12 years):
The usual initial dose is one 100 mg tablet twice daily, usually taken in the morning and in the evening.
If adequate pain relief is not achieved, the dosage may be titrated upwards to 150 or 200 mg twice daily.

Tablets should be swallowed whole with plenty of liquid. Xymel Prolonged Release tablets may be taken without regard to food.

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

Elderly patients:
The usual dosages may be used. In volunteers over 75 years of age, the elimination half-life of tramadol was increased by 17% following oral administration.

Renal impairment/renal dialysis:
As the elimination of tramadol may be prolonged in these patients, use of Xymel capsules may be more appropriate. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance <10ml/min). As tramadol is only removed very slowly by haemodialysis or haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

Hepatic impairment:
As the elimination of tramadol may be prolonged, use of tramadol capsules may be more appropriate.

Children under 12 years:
Not recommended.

4.3 Contraindications

Tramadol hydrochloride prolonged release tablets must not be taken in cases of:
- hypersensitivity to tramadol or to any of the excipients of Tramadol hydrochloride prolonged release tablets.
- acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.
- concurrent administration of monoamine oxidase inhibitors or within two weeks of their withdrawal.

4.4 Special warnings and precautions for use

Drug dependence may occur after treatment with tramadol.

Tramadol hydrochloride prolonged release tablets are not suitable as a substitute in opioid-dependent patients. Although it is an opioid antagonist, tramadol cannot suppress morphine withdrawal symptoms.

Tramadol hydrochloride prolonged release tablets 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.

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.

In common with other opioid analgesics 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.

Simultaneous administrations with cimetidine, an enzyme inhibitor, is associated with clinically insignificant changes in absolute 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 an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

4.6 Pregnancy and lactation

Pregnancy: There is inadequate evidence available on the safety of the drug in human pregnancy, but it has been in wide use for many years without apparent ill consequences. Animal studies have not revealed teratogenic or embryotoxic effects. As tramadol crosses the placental barrier, use during pregnancy should only be considered if there is no safer alternative.

Lactation: Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dose given to the mother.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Most frequently reported adverse events are nausea, sedation, dizziness, vomiting, headache, diaphoresis, skin rash, dry mouth and infrequently respiratory depression. Tramadol may also cause constipation, pruritus, 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, 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

Symptoms:
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 airways 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

Pharmacotherapeutic group: Analgesics, opioids.
ATC-Code: N02AX02.

Tramadol is a centrally acting analgesic. It is a non-selective pure agonist at mu-, delta- and kappa-opioid receptors with higher affinity for the mu-receptors.

Other mechanisms that may contribute to its analgesic effect are the inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

5.2 Pharmacokinetic properties

After oral administration, tramadol is almost completely absorbed. The absolute bioavailability is approximately 70% following a single dose and increased to approximately 90% at steady state.

C_{max} (141 ± 40ng/ml) is reached 4.9hrs after oral administration of tramadol 100 mg prolonged release tablets and 4.8 hrs (C_{max} 260 ± 62ng/ml) after oral administration of the 200 mg tablet.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The elimination half life of t½ ß is

5–7 hrs irrespective of the mode of administration.
In patients over 75 years the elimination half life of tramadol was increased by 17% following oral administration. The total clearance is 710 ml/min and may be reduced in elderly patients.

Since tramadol is eliminated both metabolically and renally, the terminal half life t½,ß may be prolonged in impaired hepatic or renal function. However, the increase in the t½,ß is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t½,ß tramadol was a mean of 13.3 ± 4.9 hrs after administration of tramadol capsules; in patients with renal insufficiency (creatinine clearance ≤ 5 ml/min) it was 11.0 ± 3.2 hrs after administration of tramadol capsules.

5.3 Preclinical safety data

In single and repeat dose toxicity studies (rodents and dogs) exposure to tramadol 10 times that expected in man is required before toxicity (hepatoxicity) is observed.
Symptoms of toxicity are typical of opioids and include restlessness, ataxia, vomiting, tremor, dyspnoea and convulsions.

Exposure to tramadol (≥ that expected in man) in lifetime toxicity studies in rodents did not reveal any evidence of carcinogenic hazard, and a variety of *in vitro* and *in vivo* mutagenicity tests were negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Hypromellose 15000
Microcrystalline cellulose
Povidone
Silica, colloidal anhydrous
Magnesium Stearate

Film coat:
Macrogol 6000
Hypromellose 5
Talc
Polyacrylate dispersion 30 %
Sunset yellow lake (E110)
Quinoline yellow lake (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Pack type: Blister (PVC (transparent, glassclear bluish or white-opaque) and aluminium foil).

Pack size: Blister packs of 10,15,20,30,40,45,50,60,100 and 100 X 1 (unit dose) tablets.

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

Kellpharm Ltd
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8 MARKETING AUTHORISATION NUMBER

PA 1044/4/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 July 2005

10 DATE OF REVISION OF THE TEXT