SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xymel 50 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg tramadol hydrochloride.

Excipients: Contains Lactose monohydrate 103.0 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsules.

Green and yellow, size 2, hard gelatin capsule, printed 'TRA 50' and containing white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management (treatment and prevention) of moderate to severe pain.

4.2 Posology and method of administration

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. 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 section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

Adults and children over the age of 12 years

Depending upon the severity of the pain, the initial dose is 50 to 100 mg tramadol, then 50 mg to 100 mg 4-6 hourly. If tramadol is used for the treatment of acute pain, it should be taken into account that the effect starts slightly later than that of other analgesics. For acute pain an initial dose of 100 mg is usually required. For pain associated with chronic conditions, an initial dose of 50 mg is recommended. A total daily dose of more than 400 mg is not usually required.

Xymel 50 should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Xymel 50 mg is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Geriatric patients

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In 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 insufficiency

In patients with impaired hepatic or renal function the elimination of tramadol may be prolonged. In these patients prolongation of dosage intervals should be carefully considered according to the patient's requirements. Further guidance is below.

It is recommended that the usual initial dosage be used and when repeated dosing is required the interval between doses is extended by a factor of 2. Subsequent dosing should be adjusted dependent on the frequency of recurrence of pain.

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

Children aged under 12 years
On account of their high dosage strength Xymel 50 mg capsules are not recommended for use in children under 12 years.

Route of administration: Oral. Capsules should be swallowed whole, not divided or chewed with sufficient liquid.

4.3 Contraindications

Hypersensitivity to tramadol or any of the excipients (see section 6.1). Acute intoxication with alcohol, hypnotics, analgesics, opioids, or psychotropic medicinal products. Tramadol should not be administered to patients concomitantly with monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5). Use in patients with epilepsy that is not adequately controlled by treatment. Use in narcotic withdrawal treatment.

4.4. Special warnings and precautions for use

Warnings
At therapeutic doses withdrawal symptoms have been reported at a frequency of 1 in 8,000. Tramadol has the potential to cause physical dependence at therapeutic doses (see "Side effects"). Reports of dependence and abuse have been less frequent. Therefore, the clinical need for continued analgesic treatment should be reviewed regularly.

Drug dependence may occur after treatment with tramadol.

In patients with a tendency for drug abuse or dependence, treatment should be for short periods and under strict medical supervision.

In patients sensitive to opiates the product should only be used with caution.

Precautions
Xymel 50 should be used with particular caution in opioid-dependent patients, patients with a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, 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 severe respiratory depression, if CNS depressant drugs are being administered concomitantly (see section 4.5) or if the recommended dose is exceeded considerably (see section 4.9), since the possibility of respiratory depression cannot be excluded in these situations.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, it cannot suppress morphine withdrawal symptoms. For physical dependency, addiction and habituation: see section 4.8 Undesirable effects.

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 Xymel with such anaesthesia should be avoided.

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

seizure threshold (see section 4.5 Interactions). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

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

4.5. Interactions with other medicinal products and other forms of interaction

Concomitant administration of tramadol with monoamine oxidase inhibitors or within two weeks of their withdrawal is contraindicated (see section 4.3). In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Xymel 50.

Concomitant administration of tramadol with other centrally acting drugs including alcohol may potentiate CNS depressant effects (see section 4.8).

Simultaneous administration with cimetidine is associated with clinically insignificant changes in 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 (enzyme inducer) markedly decreases serum concentrations of tramadol to the extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

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

Signs of serotonin syndrome may be for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied (see section 4.8).

In a limited number of studies the pre – or postoperative applicable of the antiemetic 5-HT3 antagonist ondansetron increased the requirements of tramadol in patients with postoperative pain.

4.6. Fertility, pregnancy and lactation

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on safety of the drug in human pregnancy. Therefore Xymel should not be used in pregnant women.

Tramadol – administered before or during birth – does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms. During lactation about 0.1 % of the maternal dose is secreted into the milk. Xymel is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

4.7. Effects on ability to drive and use machines

Even when taken according to instructions Xymel 50 mg may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with alcohol and other psychotropic substances.

4.8. Undesirable effects

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10% of patients.

Cardiovascular disorders:
Uncommon (≥1/1000, <1/100): cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
Rare (≥1/10000, <1/1000): bradycardia, increase in blood pressure.

Nervous system disorders:
Very common (≥1/10): dizziness.
Common (≥1/100, <1/10): headache, somnolence.
Rare (≥1/10000, <1/1000): changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly *(see section 4.5, Interaction with other medicinal products and other forms of interaction),* respiratory depression may occur.

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which lower the seizure threshold *(see sections 4.4, Special warnings and precautions for use* and *4.5, Interaction with other medicinal products and other forms of interaction).*

Not Known: speech disorders.

Psychiatric disorders:
Rare (≥1/10000, <1/1000): hallucinations, confusion, sleep disturbances, anxiety and nightmares. Psychic adverse reactions may occur following administration of Xymel, which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behavior, perception disorders). Dependence may occur.

Eye disorders:
Rare (≥1/10000, <1/1000): blurred vision.
Not Known: mydriasis.

Respiratory disorders:
Rare (≥1/10000, <1/1000): dyspnoea.

Worsening of asthma has been reported, though a casual relationship has not been established

Gastrointestinal disorders:
Very common (≥1/10): nausea.
Common (≥1/100, <1/10): vomiting, constipation, dry mouth.
Uncommon (≥1/1000, < 1/100): retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea.

Skin and subcutaneous disorders:
Common (≥1/100, <1/10): sweating.
Uncommon (≥1/1000, <1/100): dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal disorders:
Rare (≥1/10000, < 1/1000): motorial weakness.

Metabolism and Nutrition Disorders:
Not Known: hypoglycaemia

Hepatobiliary disorders:
In a few isolated cases an increase in liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.

Renal and urinary disorders:
Rare (≥1/10000, < 1/1000): micturition disorders (difficulty in passing urine, dysuria and urinary retention).

General disorders:
Common (≥1/100, <1/10): fatigue.
Rare (≥1/10000, <1/1000): allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

4.9 Overdose

Symptoms
In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment
The general emergency measures apply. Keep open the respiratory tract (aspiration), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or prolonged-release formulations.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids; ATC-code N02AX02

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

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

5.2 Pharmacokinetic properties

About 90% of tramadol is absorbed after oral administration. The bioavailability of tramadol from Tramadol capsules is high (about 70%) compared with other opioid analgesics. Peak serum concentrations are achieved after about 1 to 2 hours.

The half-life of the terminal elimination phase (t½β) was 6.0 $\pm$ 1.5 h in young volunteers. Tramadol pharmacokinetics show little age dependence, the minimal changes being therapeutically irrelevant. In patients above the age of 65 years, the $t_{½}\beta$ was 6.5 $\pm$ 1.7 h on oral administration. In volunteers aged over 75 years, $t_{½}\beta$ was 7.0 $\pm$ 1.6 h on oral administration.

Since tramadol is eliminated both metabolically and renally, the terminal half-life $t_{½}\beta$ may be prolonged in impaired hepatic or renal function. However, the increase in the $t_{½}\beta$ values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis $t_{½}\beta$, tramadol was a mean of 13.3 $\pm$ 4.9 h; in patients with renal insufficiency (creatinine clearance < 5ml/min) it was 11.0 $\pm$ 3.2 h.

5.3 Preclinical safety data

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dogs' haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some *in-vitro* test systems there was evidence of mutagenic effects. *In-vivo* studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Povidone K30
Lactose monohydrate
Sodium starch glycollate
Magnesium stearate

Capsule shell components
Titanium dioxide (E171)
Gelatin
Indigotine (E132)
Erythrosin (E127)
Yellow iron oxide (E172)

Printing ink components
Colorcon 10A2 Black consisting of:
Shellac
Black iron oxide (E172)
Propylene glycol
Ammonia solution, concentrate
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.
Keep blister in the outer carton.

6.5 Nature and contents of container

Aluminium/PVC/PVDC blister packs in a carton box.

Pack sizes: 30, 50, 100, 250 and 500 capsules.

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

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary

8. MARKETING AUTHORIZATION NUMBER

PA 126/99/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorization: 5th February 1999
Date of last renewal: 5th February 2009

10. DATE OF REVISION OF THE TEXT

October 2013