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.

Excipient(s) with known effect:
Contains Lactose Monohydrate 103.0mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard gelatin capsules.

Green and yellow, size 2, hard gelatin capsule, printed with '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

Posology
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. The total daily dose of 400 mg active substance should not be exceeded, except in special clinical circumstances.

Unless otherwise prescribed, Xymel should be administered as follows:

Adults and adolescents aged 12 years and over

Acute pain: An initial dose of 100 mg is usually necessary. This can be followed by doses of 50 or 100 mg at 4-6 hourly intervals, and duration of treatment should be matched to clinical need.

Pain associated with chronic conditions: An initial dose of 50 mg is advised and then titration according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see section 4.4).

Paediatric population

Xymel capsules are not suitable for children below the age of 12 years.

Elderly
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.

Patients with renal insufficiency/dialysis and hepatic insufficiency
In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Method of administration
Oral. Capsules should be swallowed whole, not divided or chewed with sufficient liquid, with or without food.

Duration of administration
Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with tramadol 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.

4.3 Contraindications

Xymel is contraindicated

- in hypersensitivity to the active substance or any of the excipients listed in section 6.1,
- in acute intoxication with alcohol, hypnotics, analgesics, opioids, or other psychotropic medicinal products,
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see section 4.5),
- in patients with epilepsy not adequately controlled by treatment,
- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure.

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

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). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Care should be taken when treating patients with severe respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5) or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

Tolerance, psychic and physical dependence may develop, especially after long-term use. In patients with a tendency to drug abuse or dependence, treatment with tramadol should only be carried out for short periods 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.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Xymel and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Xymel concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

CYP2D6 metabolism
Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.
General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Paediatric population

Post-operative use in children
There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function
Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal insufficiency
Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Serotonin syndrome
Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.
Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

4.5 Interaction with other medicinal products and other forms of interactions

Tramadol should not be combined with MAO inhibitors (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.

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

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur.

Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

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 syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

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 application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. There is inadequate evidence available on safety of the drug in human pregnancy. Therefore tramadol 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.

Breast-feeding
Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

Fertility
Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions tramadol 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 other psychotropic substances, particularly alcohol.

4.8 Undesirable effects

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

The frequencies are defined as follows:
Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1,000, <1/100
Rare: ≥1/10,000, <1/1000
Very rare: <1/10,000
Not known: cannot be estimated from the available data

Cardiac disorders
Uncommon: cardiovascular regulation (palpitation, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
Rare: bradycardia.

Investigations
Rare: increase in blood pressure.

Vascular disorders
Uncommon: cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Metabolism and nutrition disorders
Rare: changes in appetite.
Not known: hypoglycaemia.

Respiratory, thoracic and mediastinal disorders
Rare: depression, dyspnoea.
frequency unknown: Hiccups

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.

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

Nervous system disorders
Very common: dizziness.
Common: headache, somnolence.
Rare: speech disorders, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.
Not known: Serotonin syndrome

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* and *4.5)*.

Psychiatric disorders
Rare: hallucinations, confusion, sleep disturbances, delirium, anxiety and nightmares. Psychic adverse reactions may occur following administration of tramadol, 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. 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, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

Eye disorders
Rare: miosis, mydriasis, blurred vision.

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

Skin and subcutaneous disorders
Common: hyperhidrosis.
Uncommon: dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders
Rare: motorial weakness.

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

Renal and urinary disorders
Rare: micturition disorders (dysuria and urinary retention).

Immune system disorders
Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.

General disorders and administration site conditions
Common: fatigue.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important.
It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

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. Serotonin syndrome has also been reported.

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

Mechanism of action
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.

Clinical efficacy and safety
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.

Paediatric population
Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2).

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 ($t_{½\beta}$) was 6.0 ± 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 ± 1.7 h on oral administration. In volunteers aged over 75 years, $t_{½\beta}$ was 7.0 ± 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 ± 4.9 h; in patients with renal insufficiency (creatinine clearance < 5ml/min) it was 11.0 ± 3.2 h.

Paediatric population
The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.
In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

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
Propylene Glycol
Ammonia solution, concentrate
Potassium hydroxide
Black Iron Oxide (E172)

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/099/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 February 1999

Date of last renewal: 05 February 2009

10 DATE OF REVISION OF THE TEXT

August 2021