SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xymel SR 100 mg prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 100 mg tramadol hydrochloride.

For a full list of excipients, see section 6.1.

3. PHARMACUETICAL FORM

Prolonged release film-coated tablet.

White, round, biconvex, film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment 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 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 SR prolonged release tablets may be taken without regard to food.

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

Xymel SR should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Xymel SR 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 impairment:
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. Further guidance is below.

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.

Children under 12 years:
Not recommended.

4.3. Contraindications

- Hypersensitivity to tramadol or to any of the excipients of Xymel SR
- 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
- Xymel SR must not be used for narcotic withdrawal treatment
- Severely impaired liver function
- Severely impaired renal function (creatinine clearance <10ml/min)
- In patients with epilepsy not adequately controlled by treatment.

4.4. Special warning 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 to 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. Xymel SR is not suitable as a substitute in opioid-dependent patients. Although it is an opioid antagonist, 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 tramadol). 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 "Interactions with other medicinal products and other forms of interaction").

Xymel SR should be used with particular caution in opioid-dependent patients, patients with head injury, a reduced level of consciousness of certain origin, disorders of the respiratory centre or function, 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 interactions

Tramadol should not be combined with MAO inhibitors (see section 4.3 Contraindications). 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 SR.

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

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 (an enzyme inducer) markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

The combination with mixed agonists/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.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR and ecchymoses in some patients. The mechanism behind this interaction is unknown.

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 – Undesirable effects).

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.

Serotonin syndrome can be manifested by symptoms such as confusion, restlessness, fever, sweat, ataxia, hyperreflexia, myoclonus and diarrhoea.

The analgesic effect of tramadol is in part mediated by inhibition of the re-uptake of norepinephrine and enhancement of the release of serotonin (5-HT). In a limited number of studies the pre- or

postoperative application 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 SR 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 SR 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

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

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).*

Psychiatric disorders:
Rare (≥1/10000, <1/1000): hallucinations, confusion, sleep disturbances, anxiety and nightmares. Psychic adverse reactions may occur following administration of Xymel SR, 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 sensory capacity (e.g. decision behavior, perception disorders). Dependence may occur.

Eye disorders:
Rare (≥1/10000, <1/1000): blurred vision.

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.

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 SR 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.

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

More than 90% of Xymel SR is absorbed after oral administration. The mean absolute bioavailability is approximately 70%, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30%.

Tramadol has a high tissue affinity ($V_{d,\beta}$ = 203 ± 40 l). It has a plasma protein binding of about 20%.

After administration of Xymel SR 100 mg the peak plasma concentration C_{max} = 141 ± 40ng/ml is reached after 4.9 h. After administration of Xymel SR 200 mg C_{max} 260± 62 ng/ml is reached after 4.8 hours.

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its O-desmethyl derivative are found in breast-milk (0.1% and 0.02% respectively of the applied dose).

Elimination half-life $t_{1/2,\beta}$ is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

In humans tramadol is mainly metabolised by means of N- and O-desmethylation and conjugation of the O-desmethylation products with glucuronic acid. Only O-desmethyl tramadol is pharmacologically active. There are considerable inter-individual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyl tramadol is more potent than the parent substance by the factor 2 – 4. Its half-life $t_{1/2,\beta}$ (6 healthy volunteers) is 7.9 h (range 5.4 – 9.6 h) and is approximately that of tramadol.

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. Up to now, clinically relevant interactions have not been reported.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.1 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyl tramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 ± 3.2 h and 16.9 ± 3 h, in an extreme case 19.5 h and 43.2 h respectively.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 – 300 ng/ml is usually effective.

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, clinic-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

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

Film coat:
Macrogol 6000
Hypromellose 5
Talc
Polyacrylate dispersion 30%
Titanium dioxide (E171)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store in the original package in order to protect from light.

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

Clonmel Healthcare Ltd.,
Waterford Road,
Clonmel,
Co. Tipperary.

8. MARKETING AUTHORISATION NUMBER

PA 126/99/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 29th July 2005
Date of last renewal: 29th July 2010

10. DATE OF REVISION OF THE TEXT

October 2013