Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zydol SR 200mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 prolonged-release tablet contains 200 mg tramadol hydrochloride.

Excipients: also contains lactose monohydrate *(See section 4.4, Special warnings and precautions for use)*.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Product imported from Germany:
Slightly brownish orange, biconvex tablets engraved 'T3' on one side and with manufacturer's logo on the other.

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.

Unless otherwise prescribed, Zydol SR should be administered as follows:
Adults and adolescents above the age of 12 years:
The usual initial dose is 50-100 mg tramadol hydrochloride twice daily, morning and evening. If pain relief is insufficient, the dose may be titrated upwards to 150 mg or 200 mg tramadol hydrochloride twice daily.

For dose not practicable with this strength, other strength of this medicinal product are available.

The tablets are to be taken whole, not divided or chewed, with sufficient liquid, independent of meals.

The lowest analgesically effective dose should generally be selected. Daily doses of 400 mg active substance should not be exceeded, except in special clinical circumstances.

Zydol SR should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Zydol 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.

Children
Zydol SR is not suitable for children below the age of 12 years.

Geriatric patients
A dose adjustment is not usually necessary in elderly 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 patients requirements.

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 interval should be carefully considered according to the patients requirements. In cases of severe renal and/or hepatic insufficiency Zydol SR prolonged-release tablets are not recommended.

4.3 Contraindications

Zydol is contraindicated
- in hypersensitivity to Tramadol or any of the excipients *(see section 6.1, List of excipients)*,
- in acute intoxication with alcohol, hynotics, analgesics, opioids, or psychotropic medicinal products,
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days *(see section 4.5, Interaction with other medicinal products and other forms of interaction)*,
- in patients with epilepsy not adequately controlled by treatment,
- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Zydol SR 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.

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

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 dose limit (400mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold *(see section 4.5, Interaction with other medicinal products and other forms of interaction)*. Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment with Zydol SR 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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Zydol SR 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 Zydol SR.

Concomitant administration of Zydol SR with other centrally depressant medicinal products including alcohol may potentiate the CNS effects *(see section 4.8, Undesirable effects)*.

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.

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 re-uptake inhibitors, tricyclic anti-depressants, anti-psychotics and other seizure threshold lowering medicinal products to cause convulsions.

In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs) or with MAO inhibitors. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

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, Undesirable effects).*

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.

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, Zydol 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. Zydol 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

Even when taken accordingly to instructions, Zydol SR 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.

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

Cardiovascular disorders:
uncommon: 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: bradycardia, increase in blood pressure

Nervous system disorders:
very common: dizziness
common: headache, somnolence
rare: 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), respiratory depression may occur.

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see sections 4.4 and 4.5).
not known: speech disorders

Psychiatric disorders:
rare: hallucinations, confusion, sleep disturbance and nightmares. Psychic adverse reactions may occur following administration of Zydol 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 sensorial capacity (e.g. decision behaviour, perception disorders). Dependence may occur.

Eye disorders:
rare: blurred vision
not known: mydriasis

Respiratory disorders:
*rare:*dyspnoea

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

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: sweating
uncommon: dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal 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 (difficulty in passing urine, dysuria and urinary retention)

General disorders:
common: fatigue
rare: 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 (opiods) 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 as 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 formulation.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids; ATC-code N 02 AX 02

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

More than 90% of Zydol 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 low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Tramadol has a high tissue affinity (V d,β = 203 ± 40 1). It has a plasma protein binding of about 20%.

After administration of Zydol SR 100 mg the peak plasma concentration Cmax = 141 ± 40 ng/ml is reached after 4.9 h. After administration of Zydol SR 200 mg Cmax 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 the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Elimination half-life t 1/2,β 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-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent that the parent substance by the factor 2 – 4. Its half-life t ½,β (6 healthy volunteers) is 7.9 h (range 5.4 – 9.6h) 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 excreation is 90% of the total radioactivity of the administered dose. In case of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half lives of 13.3 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyltramadol), 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 liner 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, clinicochemical 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 50mg/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 50mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125mg/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 15mg/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
Hypromellose
Magnesium stearate
Colloidal anhydrous silica
Lactose monohydrate
Macrogol 6000
Propylene glycol
Talc
Titanium dioxide (E 171)
Quinoline yellow lake (E104)
Red iron oxide (E 172)
Brown iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C
Store in the original container.

6.5 Nature and contents of container

Pack sizes of 60 tablets contained in an outer cardboard carton

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 465/189/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th April 2011

10 DATE OF REVISION OF THE TEXT