# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Zydol XL 150mg prolonged-release tablets.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150mg tramadol hydrochloride

Excipients - Contains lactose monohydrate 0.6mg

For a full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Prolonged release tablets.
The tablets are white, film coated tablets, marked ‘T 150’.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the management (treatment and prevention) of severe pain.

### 4.2 Posology and method of administration

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 & precautions for use and section 4.8, Undesirable effects).

ZYDOL-XL tablets should be taken at 24-hourly intervals and must be swallowed whole and not chewed.

The dose of Tramadol should be adjusted according to the severity of the pain and the clinical response of the individual patient. The correct dosage for any individual patient is that which controls the pain with no or tolerable side effects for a full 24 hours. It is recommended that patients are slowly titrated to higher doses to minimise transient side effects. A total oral daily dose of more than 400 mg is not usually required.

*Adults and children over 12 years*: The usual initial dose is one 150 mg tablet daily. If pain relief is not achieved, the dosage should be titrated upwards until pain relief is achieved.

*Elderly and patients with renal or hepatic impairment*: The elimination half-life of tramadol may be prolonged in these patient populations. A starting dose of 150 mg daily is recommended. Dose titration upwards should be carefully monitored.

*Children under 12 years*: Not recommended.

### 4.3 Contraindications

Hypersensitivity to tramadol or to any of the constituents of the product; acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

## 4.4 Special warnings and precautions for use

Tramadol has the potential to cause physical dependence at therapeutic doses (see section 4.8, Undesirable effects).

Tramadol is not suitable for use as a substitute in cases of opioid dependency. Although tramadol is an opioid agonist, it cannot suppress morphine withdrawal symptoms. To minimise the risk of dependence, tramadol should be used with great caution in patients with a history of addiction or dependence.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being co-administered, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses, respiratory depression has been reported infrequently.

Patients who are hypersensitive to codeine should be treated with caution as they may also be hypersensitive to tramadol.

Tramadol should be used with caution in patients with head injuries, raised intra-cranial pressure, severe hepatic or renal impairment, in shock, and in patients prone to convulsive disorders.

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

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of tramadol with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects.

Co-administration with cimetidine is associated with a small prolongation of the half-life of tramadol, but this is not clinically relevant.

Simultaneous treatment with carbamazepine may shorten the analgesic effect as a result of a reduction in serum levels of tramadol and its active metabolite.

There is an increased possibility of convulsions in patients already taking antiepileptics or in those being treated with drugs that may cause seizures.

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and anti-psychotics to cause convulsions.

Isolated cases of serotonergic syndrome have been reported with the therapeutic use of tramadol in combination with other serotonergic agents such as selective serotonin re-uptake inhibitors (SSRIs). Serotonergic syndrome can be manifested by symptoms such as confusion, restlessness, fever, sweating, ataxia, hyperreflexia, myoclonia and diarrhoea. Withdrawal of the serotonergic agent produces a rapid improvement.

Co-administered Ritonavir may increase serum concentrations of tramadol resulting in tramadol toxicity.

Digoxin toxicity has occurred rarely during co-administration of digoxin and tramadol.

MAO inhibitors: a serotinergic syndrome is likely to occur (see above). In case of recent treatment with MAOIs, treatment with tramadol should not be started until 2 weeks after cessation of treatment with MAOIs.

Other morphine derivatives: (including anti-tussives, substitution treatments), benzodiazepines, barbiturates: increased risk of respiratory depression that may be fatal in overdosage.

Mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine): the analgesic effect of tramadol which is a pure agonist may be reduced and a withdrawal syndrome may occur.

There have been isolated reports of interaction with coumarin anticoagulants resulting in increased INR and so care should be taken when commencing treatment with tramadol in patients on anticoagulants.

There is a theoretical possibility that tramadol could interact with lithium or 5HT or noradrenaline potentiating anti-depressants due to their mechanisms of action.

The analgesic effect of tramadol is in part medicated by inhibition of the re-uptake of norepinephrine and enhancement of the release of serotonin (5-HT). In studies the pre- or postoperative application of the antiemetic 5-$HT^3$ antagonist ondansetron increased the requirements of tramadol in patients with postoperative pain.

## 4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of tramadol in pregnant women. Animal studies have shown reproductive toxicity, but not teratogenic effects (see section 5.3, Preclinical safety data). Tramadol crosses the placental barrier and chronic use during pregnancy can cause withdrawal symptoms in the new-born baby. Therefore, it should not be used during pregnancy.

Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in respiratory rate which are not usually clinically relevant.

During lactation very small amounts of tramadol and its metabolites (approximately 0.1% of an intravenous dose) are found in human breast milk.
Therefore tramadol should not be administered during breast feeding**.**

## 4.7 Effects on ability to drive and use machines

Tramadol may cause drowsiness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

## 4.8 Undesirable effects

The following frequency categories form the basis for classification of the undesirable effects:

Very common (≥1/10)>
Common (≥1/100 to <1/10)>
Uncommon (≥1/1,000 to 1/100)>
Rare (≥1/10,000 to <1/1,000)>
Very rare (<1/10,000)>
Not known (cannot be estimated from the available data)

| | **Very Common** | **Common** | **Uncommon** | **Rare** | **Very Rare** | **Not known** |
|---|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | Blood dyscrasias | | |
| **Immune system disorders** | | | | Hypersensitivity Anaphylactic reaction | | |
| **Metabolism and nutritional** | | | | Anorexia | | |

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| **disorders** | | | | | | |
| **Psychiatric disorders** | | | | Hallucinations<br>Nightmares<br>Euphoric mood<br>Dysphoria<br>Decreased activity<br>Increased activity<br>Confusional state<br>Abnormal thinking | | Drug dependence |
| **Nervous system disorders** | Dizziness | Somnolence | Headache | Paraesthesia<br>Cognitive disorders<br>Sensory disturbances<br>Convulsions | | |
| **Eye disorders** | | | | Visual impairment | | |
| **Cardiac disorders** | | | Palpitations<br>Tachycardia | Syncope<br>Bradycardia | | |
| **Vascular disorders** | | | Decrease in blood pressure<br>Cardiovascular collapse | Hypertension<br>Flushing | | |
| **Respiratory, thoracic and mediastinal disorders** | | | | Dyspnoea<br>Worsening of asthma<br>Respiratory depression<br>Bronchospasm | | |
| **Gastro-intestinal disorders** | Nausea | Vomiting<br>Dry mouth | Retching<br>Constipation | Diarrhoea | | |
| **Hepatobiliary disorders** | | | | Hepatic enzymes increased | | |
| **Skin and subcutaneous tissue disorders** | | Hyperhidrosis | Pruritus<br>Rash<br>Urticaria | Angioedema | | |
| **Renal and urinary disorders** | | | | Micturition disorders<br>Urinary retention | | |
| **Musculoskeletal and connective tissue disorders** | | | | Muscular weakness | | |
| **General disorders and administration site conditions**<br>**Investigations** | | Fatigue | | | | |

Withdrawal reactions, similar to those occurring during opiate withdrawal, may occur and include: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

## 4.9 Overdose

Symptoms of overdosage are typical of other opioid analgesics and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression which may - in severe cases - result in a fatal outcome.

*Treatment of tramadol overdosage*: Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. Fits can be controlled with diazepam.

In the case of massive overdosage, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. ZYDOL-XL tablets will continue to release and add to the tramadol load for up to 24 hours after administration and the management of tramadol overdosage should be modified accordingly.

For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should only be administered for tramadol overdosage when there is clinically significant respiratory or circulatory depression. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on tramadol. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

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

Emptying the gastric contents is useful to remove any unabsorbed drug, particularly when a prolonged release formulation has been taken.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other opioids
ATC code: N02A X02

Tramadol is a centrally acting analgesic. It is a non selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms that may contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline and an enhancement of 5HT release.

## 5.2 Pharmacokinetic properties

Following oral administration of a single dose, tramadol is almost completely absorbed and the absolute bioavailability is approximately 70%. Tramadol is metabolised to O-desmethyltramadol, which has been shown to have analgesic activity in rodents. The elimination half life of tramadol is around 6 hours, although this is extended to around 16 hours following prolonged absorption from the ZYDOL-XL tablet.

Following administration of one ZYDOL-XL tablet 200 mg in the fasting state, a mean peak plasma concentration (Cmax) of 192 ng.ml-1 was attained. This was associated with a median tmax of 6 hours (range 4-8 hours). The availability of tramadol from the ZYDOL-XL tablet 200 mg was complete when compared with an immediate release tramadol solution 100 mg. In the presence of food, the availability and controlled release properties of ZYDOL-XL tablets were maintained, with no evidence of dose-dumping.

A single dose-proportionality study has confirmed a linear pharmacokinetic response (in relation to tramadol and O-desmethyltramadol) following administration of the 200 mg, 300 mg and 400 mg tablets. A steady state study has confirmed the dose-adjusted bioequivalence of the 150 mg and 200 mg tablets administered once daily.

A further steady state study has demonstrated that immediate release tramadol tablets 50 mg, administered 6-hourly, provided plasma concentrations that were greater than would have been anticipated following administration of a single dose. This observation is consistent with a non-linear elimination of the drug substance. In contrast, the plasma concentrations from ZYDOL-XL tablet 200 mg administered once-daily were in line with single dose data, confirming that the controlled delivery of tramadol from ZYDOL-XL minimises the non-linearity associated with faster-releasing preparations. The more predictable plasma concentrations may lead to a more manageable dose titration process.

## 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential.

Studies in rats and rabbits have revealed no teratogenic effects. However, embryotoxicity was shown in the form of delayed ossification. Fertility, reproductive performance and development of offspring were unaffected.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Hydrogenated vegetable oil
Talc
Magnesium stearate
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 4000

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

Three years.

## 6.4 Special precautions for storage

Do not store above $30^0$C.

## 6.5 Nature and contents of container

1. PVC blisters with aluminum backing foil (containing 2, 7, 14, 28, 30 or 56 tablets).

2. Polypropylene containers with polyethylene lids (containing 2, 7, 14, 28, 30 or 56 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

Napp Pharmaceuticals Ltd.,
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## 8 MARKETING AUTHORISATION NUMBER

PA 913/21/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 1999
Date of last renewal: 24 May 2009

## 10 DATE OF REVISION OF THE TEXT

April 2011