SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZYDOL SR 200 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 200 mg tramadol hydrochloride.

Excipient: Each prolonged-release tablet contains 2.5 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets

Slightly brownish orange coloured, round biconvex film-coated tablets marked with manufacturer's logo on one side and T3 on the other side.

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. The total daily doses of 400 mg tramadol hydrochloride should not be exceeded, except in special clinical circumstances.

Unless otherwise prescribed, ZYDOL SR should be administered as follows:

<u>Adults and adolescents above the age of 12 years</u>

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 (see section 5.1).

<u>Children</u>

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

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

Method of administration

The tablets are to be taken whole, not divided or chewed, with sufficient liquid, with or without food.

Treatment goals and discontinuation

Before initiating treatment with ZYDOL SR, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

4.3 Contraindications

ZYDOL SR 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

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 medicinal product should only be used with caution.

Concomitant use of ZYDOL SR and sedating medicinal products such as benzodiazepines or related substances, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe ZYDOL SR concomitantly with sedating medicinal products, the lowest effective dose of ZYDOL SR should be used, and the duration of the concomitant 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).

Care should be taken when treating patients with 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.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnea (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.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol hydrochloride exceed the recommended upper daily limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see section 4.5*)*. Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

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.

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as ZYDOL SR. Repeated use of ZYDOL SR can lead to opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of ZYDOL SR may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders

(including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with ZYDOL SR and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

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%

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.

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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or 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).
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.

Centrally acting medicinal products/central nervous system (CNS) depressants, including alcohol and CNS depressant narcotic drugs.

The concomitant use of ZYDOL SR with sedating medicinal products such as benzodiazepines or other respiratory or CNS depressants (e.g. other opioids, antitussives or substitution treatments, barbiturates, antipsychotics, H1-antihistamines, alcohol) increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect (see section 4.8).

Therefore, if a decision is made to prescribe ZYDOL SR concomitantly with respiratory or CNS depressants, the lowest effective dose of ZYDOL SR should be used, and the duration of the concomitant treatment should be as short as possible.

The concomitant use of ZYDOL SR with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

Anticholinergics
Concomitant administration of ZYDOL SR with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse 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.

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 product (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.

4.6 Pregnancy and lactation

Pregnancy
Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. There is inadequate evidence available on the safety of tramadol 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 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

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

Respiratory, thoracic and mediastinal disorders:

Rare: respiratory depression, dyspnoea

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 causal relationship has not been established.
Not known: Hiccups.

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 can lower the seizure threshold (see sections 4.4 and 4.5).

Psychiatric disorders:

Rare: hallucinations, confusion, sleep disturbance 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 behaviour, perception disorders). Drug dependence may occur. Symptoms of drug withdrawal syndrome, 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: constipation, dry mouth, vomiting

Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea

Skin and subcutaneous tissue 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)

Metabolism and nutrition disorders:

Not known: hypoglycaemia

General disorders:

Common: fatigue

Drug dependence

Repeated use of ZYDOL SR can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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 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, respiratory depression up to respiratory arrest and death.
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 due to tramadol 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 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: N02 AX02

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.

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

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 the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

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

After administration of ZYDOL SR 100 mg the peak plasma concentration C_{max} =141 ± 40 ng/ml is reached after 4.9 h; after administration of ZYDOL 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 the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Elimination half-life $t_{1/2,ß}$ 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 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.
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 13.3 $\pm$ 4.9 h (tramadol) and 18.5 $\pm$ 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 $\pm$ 3.2 h and 16.9 $\pm$ 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.

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

Tablet core:
Microcrystalline cellulose
Hypromellose 100 000 mPa's
Magnesium stearate
Colloidal anhydrous silica

Film coating:
Hypromellose 6 mPa's
Lactose monohydrate
Macrogol 6000
Propylene glycol
Talc
Titanium dioxide (E171)
Quinoline yellow lake (E104) aluminium salt
Red iron oxide (E172)
Brown iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30ºC
Store in the original container

6.5 Nature and contents of container

PVC/PVDC/foil blister packs of 2, 4 or 10 tablets. (Sample/starter packs)
PVC/PVDC/foil blister packs of 30 or 60 tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Grünenthal Pharma Ltd.
4045 Kingswood Road
Citywest Business Park
Citywest, Co. Dublin
Ireland

8. MARKETING AUTHORISATION NUMBER

PA 2242/5/5

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st February 1997
Date of last renewal: 21st February 2007

10. DATE OF REVISION OF THE TEXT

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