PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

ZYTRAM® 150 mg prolonged release tablets

ZYTRAM® 200 mg prolonged release tablets

ZYTRAM® 300 mg prolonged release tablets

ZYTRAM® 400 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZYTRAM 150 mg prolonged release tablet contains 150 mg of tramadol hydrochloride.

Each ZYTRAM 200 mg prolonged release tablet contains 200 mg of tramadol hydrochloride.

Each ZYTRAM 300 mg prolonged release tablet contains 300 mg of tramadol hydrochloride.

Each ZYTRAM 400 mg prolonged release tablet contains 400 mg of tramadol hydrochloride.

Excipients with known effect:

Each ZYTRAM 150 mg prolonged release tablet contains 0,60 mg lactose monohydrate (see section 4.4).

Each ZYTRAM 200 mg prolonged release tablet contains 1,00 mg lactose monohydrate (see section 4.4).

Each ZYTRAM 300 mg prolonged release tablet contains 1,40 mg lactose monohydrate (see section 4.4).

Each ZYTRAM 400 mg prolonged release tablet contains 1,80 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet

ZYTRAM 150 mg is a white film coated, oval shaped tablet approximately 13 mm in length marked T 150 on one side.

ZYTRAM 200 mg is a white film coated, oval shaped tablet approximately 15 mm in length marked T 200 on one side.

ZYTRAM 300 mg is a white film coated, oval shaped tablet approximately 17 mm in length marked T 300 on one side.

ZYTRAM 400 mg is a white film coated, oval shaped tablet approximately 19 mm in length marked T 400 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

These tablets are indicated in adults and adolescents aged 12 years and above.

4.2 Posology and method of administration

Route of administration

Oral use

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 correct dosage per individual patient is that which controls the pain, with no or tolerable side effects, for a full 24 hours. Patients transferring from immediate release tramadol preparations should have their total daily dose calculated, and start on the nearest dose in the ZYTRAM range. It is recommended that patients are slowly titrated to higher doses to minimise transient side effects. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see section 4.4). A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

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.

Special populations

Elderly 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 impairment/dialysis

In patients with renal impairment the elimination of tramadol is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patient's requirements. As tramadol is only removed very slowly by haemodialysis or by haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

Patients with hepatic impairment

In patients with hepatic insufficiency the elimination of tramadol hydrochloride is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according

to the patient's requirements. In cases of severe hepatic insufficiency ZYTRAM tablets are not recommended.

Paediatric population

Paediatric population under 12 years of age

The safety and efficacy of ZYTRAM tablets has not been established and the product should not be used in children.

On account of the high dosage strength, ZYTRAM tablets should not be used in children below the age of 12 years.

Duration of treatment

Under no circumstances should ZYTRAM tablets be given for longer than absolutely necessary. If the nature and severity of the disease require long-term pain treatment, careful checks should be carried out initially and at regular intervals to assess efficacy and adverse events and to what extent further treatment with ZYTRAM tablets is necessary.

Method of administration

ZYTRAM should be taken at 24-hourly intervals and must be swallowed whole and not broken, crushed or chewed.

4.3 Contraindications

ZYTRAM is contraindicated in:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines;
- patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal;
- narcotic withdrawal treatment;

- postoperative pain management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy;
- patients with epilepsy;
- patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease;
- pregnant and breastfeeding women (see section 4.6).

4.4 Special warnings and precautions for use

Tolerance, psychic and physical dependence may develop, especially after long-term use. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

There is potential for abuse and development of psychological dependence to opioid analgesics, including tramadol, therefore the clinical need for continued analgesic treatment should be reviewed regularly. Treatment should be for short periods and under strict medical supervision. These tablets should be used with particular care in patients with a history of alcohol and drug abuse.

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

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit. 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 section 4.5). Tramadol should therefore be used with caution in patients prone to convulsive disorders.

Tramadol should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function and in patients in shock.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant medicines (see section 4.5) are being administered, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain (i.e. less focal), or pain from ordinary (i.e. ono-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible.

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 %

Lactose

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.

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.

Hyponatraemia

Hyponatraemia has been reported with the use of ZYTRAM, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatraemia. This hyponatraemia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with

discontinuation of ZYTRAM and appropriate treatment (e.g. fluid restriction). During ZYTRAM treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

4.5 Interaction with other medicines and other forms of interaction

ZYTRAM should not be combined with MAO inhibitors, or used within 14 days of withdrawal of 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 of the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with ZYTRAM.

Concurrent administration of tramadol with medicines that depress the CNS may lead to an increased risk of respiratory depression, profound sedation, coma and death. Medicines which depress the CNS include but are not limited to: other opioids (including antitussives and substitution therapy), anxiolytics, hypnotics and sedatives (including benzodiazepines), antipsychotics, antidepressants, phenothiazines, barbiturates and alcohol.

ZYTRAM can induce convulsions and increase the potential for selective serotonin re-uptake 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 ZYTRAM and serotonergic medicines, 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 ºC and inducible or ocular clonus.

Withdrawal of the serotonergic medicines usually brings about a rapid improvement.

Treatment depends on the type and severity of the symptoms.

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

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

Co-administered ritonavir may increase serum concentration of tramadol resulting in tramadol toxicity.

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

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.

Caution should be exercised during concomitant treatment with ZYTRAM and warfarin-like medicines due to reports of increased International Normalised Ration (INR) with major bleeding and ecchymoses in some patients.

The analgesic effect of tramadol is in part mediated by inhibition of the re-uptake of noradrenaline (norepinephrine) and enhancement of the release of serotonin (5-HT). In 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

Pregnancy

Safety during pregnancy and lactation has not been established.

Animal studies have shown effects on organ development, ossification and neonatal mortality (see section 5.3). Tramadol crosses the placental barrier and chronic use during

pregnancy can cause withdrawal symptoms in the new-born baby. Therefore, ZYTRAM 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.

Breastfeeding

Tramadol is excreted in breast milk. Tramadol should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

In clinical studies, the most common adverse events observed with ZYTRAM were those typical of opioids and mainly concerned the gastrointestinal and nervous system. In addition, adverse effects concerning the skin were noted. Adverse effects affecting the gastrointestinal system included nausea, vomiting, constipation, dry mouth, dyspepsia, and abdominal pain. Adverse effects affecting the nervous system included drowsiness, dizziness, insomnia, confusion, sedation, somnolence, headache, fatigue, and paraesthesia. Adverse effects affecting the skin included pruritus and flushing. In the studies in patients taking ZYTRAM these adverse reactions were in general of mild to moderate severity and partly decreased in incidence during use.

b. Tabulated list of adverse reactions

The reactions are listed as MedDRA preferred term by system organ class and absolute frequency.

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).

Immune System disorders	
Rare	Hypersensitivity, Anaphylactic and anaphylactoid responses
Metabolism and nutrition disorders	
Rare	Decreased appetite
Not known	Hypoglycaemia
Psychiatric disorders	
Uncommon	Medicine dependence
Rare	Hallucinations, Nightmare, Mood altered, Euphoric mood, Dysphoria, Decreased activity, Illusion, Confusional state
Nervous system disorders	
Very Common	Dizziness
Common	Somnolence
Uncommon	Headache
Rare	Paraesthesia, Psychomotor hyperactivity, Cognitive disorder, Sensory disturbance, Judgement impaired, Seizure
Eye disorders	
Rare	Blurred vision
Cardiac disorders	
Uncommon	Palpitations, Tachycardia
Rare	Bradycardia
Vascular disorders	
Uncommon	Orthostatic hypotension, Hypotension, Circulatory collapse
Rare	Hypertension, Flushing
Respiratory, thoracic and mediastinal disorders	

Rare	Dyspnoea, Worsening of asthma, Respiratory depression, Bronchospasm, Wheezing
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, Dry mouth
Uncommon	Retching, Constipation, Abdominal discomfort
Rare	Diarrhoea
Hepatobiliary disorders	
Very Rare	Hepatic enzyme increased
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
Uncommon	Pruritus, Rash, Urticaria
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Rare	Muscular weakness
Renal and urinary disorders	
Rare	Micturition disorder, Dysuria, Urinary retention
General disorders and administration site conditions	
Very Rare	Medicine withdrawal syndrome which may include: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor, gastrointestinal symptoms
Not known	Asthenia

c. Description of selected adverse reactions

Tolerance, psychic and physical dependence may develop, especially after long-term use. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.2).

d. Paediatric population

Neonatal drug withdrawal syndrome may occur in infants born to mothers taking tramadol, however the frequency is unknown (see section 4.6).

As these tablets are made using an insoluble matrix from which the active ingredient is gradually released, the patient may notice the matrix in their faeces.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8, or you can report directly to the company at ZADrugsafety@mundipharma.co.za.

4.9 Overdose

Symptoms

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

Management

The general emergency measures apply. Keep open the airway, prevent aspiration and maintain respiration and circulation depending on the symptoms. Suitable measures should be taken to avoid aspiration dangers.

The pure opioid antagonists such as naloxone are specific antidotes against symptoms from opioid overdose induced by tramadol, though it will not antagonise tramadol's inhibitory effects on MAO reuptake or serotonin releasing effects. Other supportive measures should be employed as needed. Naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam. In case of oral intake of overdose, consider activated

charcoal if the patient presents within one hour of ingestion of tramadol, provided the patient's airway can be protected.

Although it may seem reasonable to assume that later administration of activated charcoal may be beneficial for prolonged-release preparations and medicines that slow gastric emptying, there is no clinical trial evidence to support this.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.2.9 Other analgesics

ATC Code: N02AX02

Mechanism of action

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 contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline (norepinephrine) and serotonin.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a single dose, tramadol is almost completely absorbed, and the absolute bioavailability is approximately 70 %.

Biotransformation

Tramadol is metabolised to O-desmethyltramadol, which has been shown to have analgesic activity in rodents. 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.

Elimination

The elimination half-life of tramadol is around 6 hours, although this is extended to around 16 hours following prolonged absorption from the ZYTRAM tablet.

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

Linearity/non-linearity

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. This study also confirmed that the ZYTRAM tablet 150 mg provided an equivalent peak concentration and extent of availability of tramadol to an immediate release capsule 50 mg administered 8-hourly. On this basis it is recommended that patients receiving immediate release tramadol should be transferred initially to the nearest daily dose of ZYTRAM tablets. It may be necessary to titrate the dose thereafter.

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 active substance. In contrast, the plasma concentrations from ZYTRAM tablet 200 mg administered once-daily were in line with single dose data, confirming that the controlled delivery of tramadol from ZYTRAM 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.

Reproductive and developmental toxicity

No effects of tramadol have been observed on male or female fertility in rats. Foetal malformations occurred in a rat developmental study in the presence of maternal toxicity and mortality. No developmental effects were observed in the rat at 20 mg/kg/day when plasma concentrations of tramadol and O-desmethyltramadol were 2,1 x and 2,0 x the estimated mean clinical C_{max} and 0,6 x and 0,7 x the estimated mean clinical AUC_t at the maximum recommended dose of ZYTRAM 400 mg once daily. When female rats were treated during gestation and lactation there was increased pup mortality and decreased body weights during lactation for the offspring at maternally toxic dose levels of 60 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hydrogenated vegetable oil, magnesium stearate, talc

Film coat

Hypromellose (E464), lactose monohydrate, macrogol 4000, titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

PVC blisters with aluminium backing foil (containing 28 tablets).

6.6 Special precautions for disposal

None

7 HOLDER OF CERTIFICATE OF REGISTRATION

Mundipharma (Pty) Ltd,

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Park Lane, Century City,

7441, Cape Town,

South Africa

8 REGISTRATION NUMBER(S)

ZYTRAM® 150 mg: 54/2.9/0483

ZYTRAM® 200 mg: 54/2.9/0484

ZYTRAM® 300 mg: 54/2.9/0485

ZYTRAM® 400 mg: 54/2.9/0486

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 August 2023

10 DATE OF REVISION OF THE TEXT

8 August 2023

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