1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

TREMADOL® 50mg, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Tramadol dihydrochloride ..... 50,00 mg

Excipients:

Sodium Starch Glycolate (type A) ..... 10,15 mg
Microcrystalline cellulose ..... 36,75 mg
Mannitol ..... 76,35 mg
Magnesium stearate ..... 1,05 mg
Colloidal Anhydrous Silica ..... 0,70 mg

For one tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White circular biconvex tablet, engraved TML on one side and COOPER on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of moderate to severe pain for adult.

4.2. Posology and method of administration

Method of administration

For oral administration

Posology

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose should generally be selected.

This product must never be used for longer than therapeutically absolutely necessary. Should prolonged pain treatment according to the nature and severity of the illness be necessary, a careful evaluation should be carried out at short regular intervals (if necessary by instituting treatment pauses) to check whether or to what extent prolonged treatment is medically necessary.

Acute Pain:

An initial dose of 100mg (2 tablets) is usually necessary. This can be followed by doses of 50 or 100 mg (1 to 2 tablets) at 4 - 6 hourly intervals, The total daily dose of 400 mg active substance should not be exceeded (8 tablets),

Chronic pain:

An initial dose of 50 or 100mg (1 or 2 tablets) is usually necessary. This can be followed by doses of 50 or 100 mg (1 to 2 tablets) at 4 - 6 hourly intervals, The total daily dose of 400 mg active substance should not be exceeded (8 tablets),

Children

This medicine is not contraindicated for children below the age of 15 years (see section 4.3).

Eldery 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 insufficiency

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.

4.3. Contraindications

TREMADOL 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, particularly with linezolid and methylene blue (see section 4.5)
- In case of severe respiratory failure;
- in children under 15 years of age;
- in patients with epilepsy not adequately controlled by treatment (see section 4.4),
- for use in narcotic withdrawal treatment.

This medicine should not generally be used:

- during pregnancy.

4.4. Special warnings and precautions for use

Special warnings

Tramadol 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 opioid-dependent patients and in patients with a history of abuse or dependence, treatment should be of short duration and 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.

Tolerance,physical and psychological dependence may develop, especially after long-term use. The clinical necessity of an analgesic treatment should be reassessed on a regular basis (see section 4.2). Cases of addiction and abuse have been reported (see section 4.8).

Symptoms of withdrawal, similar to those occurring during opioid withdrawal, may occur even at therapeutic doses and for short-term treatments (see section 4.8). Symptoms of withdrawal can be avoided by gradually decreasing doses when discontinuing treatment, especially after long periods of treatment.

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

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 apnoea (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.

The combination of tramadol with morphine agonist-antagonists (buprenorphine, nalbuphine, pentazocine) and carbamazepine are not recommended (see section 4.5).

Alcohol use during treatment is discouraged.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol dihydrochloride exceed the recommended upper daily dose limit (400 mg of tramadol dihydrochloride). 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 be only treated with tramadol if there are compelling circumstances.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

The concomitant use of TREMADOL with sedative medicines such as benzodiazepines or other related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe TREMADOL concomitantly with sedative medicines, the lowest effective dose should be used, and the treatment duration 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).

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.

Serotonin syndrome is likely if any of the following symptoms are observed:

- Spontaneous clonus,
- Inducible or ocular clonus accompanied by agitation or diaphoresis,
- Tremor and hyperreflexia,
- Hypertonia and body temperature > 38°C and inducible or ocular clonus.

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.

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, even at recommended doses, of side effects relating to opioid toxicity.

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 literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but potentially 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.

Precautions for use

Tramadol should only be used after a careful assessment of the risk benefit ratio, depending on the origin of the pain and the patient's profile (see section 5.3).

Tramadol should be used with caution in the elderly because of the risk of falling and loss of consciousness.

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

Pharmacokinetic studies have so far shown that concomitant or previous administration of cimetidine (enzymatic inhibitor) is unlikely to cause clinically relevant interactions.

Drugs that cause serotonin syndrome

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).

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).

Other drugs known to inhibit CYP3A4 such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) and probably also metabolism of the active O-demethylated metabolite. The clinical significance of such interaction has not been studied (see section 4.8).

Medicines lowering the seizure threshold

The joint use of proconvulsant drugs or lowering the seizure threshold, must be carefully considered, because of the severity of the risk. These medicines are represented by most antidepressants (imipraminic, selective serotonin reuptake inhibitors), neuroleptics (phenothiazines and butyrophenones), mefloquine, chloroquine, bupropion, tramadol and fluoroquinolones.

Sedative medicines such as benzodiazepines or related drugs

Consideration should be given to the fact that many drugs or substances can add up to their depressant effects of the central nervous system and help to reduce alertness. These include opioid derivatives (analgesics, antitussives and substitution treatments), neuroleptics, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines (for example, meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, Mianserin, mirtazapine, trimipramine), sedative H1 antihistamines, central antihypertensive agents, baclofen and thalidomide.

Concomitant use of opioids with sedative drugs such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma, and death due to an additive central nervous system depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Contraindicated associations (see section 4.3)

+ Irreversible MAOIs (iproniazide)

Risk of a serotonin syndrome, a potentially fatal condition (see sections 4.4 and 4.8).

Respect a delay of two weeks between discontinuation of MAOI and the start of treatment with tramadol and at least one week between the discontinuation of tramadol and the start of MAOI.

Associations not recommended

+ Morphine agonist-antagonists (buprenorphine, nalbuphine, pentazocine)

Decreased analgesic effect by competitive blockade of receptors, with the risk of developing withdrawal syndrome.

+ Alcohol (beverage or excipient)

Alcohol increases the sedative effect of opioid analgesics.

Impaired alertness can make driving vehicles and using machines dangerous.

Avoid taking alcoholic beverages and medicines containing alcohol

+ Carbamazepine

Risk of decreased plasma concentrations of tramadol.

Simultaneous or previous administration of carbamazepine (enzymatic inducer) may reduce analgesic effects and shorten the duration of action of tramadol.

+ Reversible MAOI A including linezolid and methylene blue

Risk of a serotonin syndrome, a potentially fatal condition (see sections 4.4 and 4.8).

If the association cannot be avoided, very close clinical monitoring. Start the combination at the recommended minimum dosages.

+ Partial antagonist morphine

Risk of decreased analgesic effect.

+ Naltrexone

Risk of decreased analgesic effect.

+ Sodium oxybate

Increased central vacuum

Impaired alertness can make driving vehicles and using machines dangerous.

Associations faisant l'objet de précautions d'emploi

+ Antivitamin K

Risk of increased effect of antivitamin K and hemorrhagic risk. More frequent monitoring of INR. Possible adaptation of the dosage of antivitamin K during treatment with tramadol and after discontinuation.

Associations to consider

+ Other morphine analgesics agonists, antitussives morphine-like (dextromethorphan, noscapine, pholcodine), true morphine antitussives (codeine, ethylmorphine)

Increased risk of respiratory depression which can be fatal in case of overdose.

+ Other drugs lowering the epileptogenic threshold

Increased risk of convulsions.

+ Other sedative drugs

Increased of the central depression.

Impaired alertness can make driving vehicles and using machines dangerous.

+ Benzodiazepines and related

Increased risk of respiratory depression which may be fatal in case of overdose.

+ Barbiturates

Increased risk of respiratory depression which may be fatal in case of overdose.

+ IMAO-B

Risk of a serotonin syndrome, a potentially fatal condition (see sections 4.4 and 4.8).

+ Selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)

Risk of convulsions and / or serotonin syndrome, a potentially fatal condition (see sections 4.4 and 4.8).

+ Venlafaxine

Risk of convulsions and / or serotonin syndrome, a potentially fatal condition (see sections 4.4 and 4.8).

+ Buproprion

Increased plasma concentrations of tramadol by decreasing of its hepatic metabolism by bupropion.

In addition, there is a risk of convulsions by adding the effects of the two drugs.

+ Ondansetron

Reduction in the intensity and duration of the analgesic effect of tramadol and risk of reduction of the antiemetic effect of ondansetron.

4.6. Fertility, pregnancy and lactation

Pregnancy

Animal studies using tramadol have showed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects have not been demonstrated. Tramadol crosses the placenta.

There is inadequate evidence regarding the safety of tramadol in human pregnancy. Therefore, tramadol should not be used in pregnant women.

Administered before or during childbirth, tramadol does not modify uterine contractility.

Tramadol may cause changes in respiratory rate in neonates, which are generally without adverse clinical consequences. Prolonged use during pregnancy may lead to withdrawal syndrome in the newborn.

Breast-feeding

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate postpartum period, for maternal oral daily dosage of up to 400 mg, corresponds to a mean amount of tramadol ingested by breastfed infant of 3% of the maternal weight-adjusted dosage. Therefore, tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breastfeeding 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, TREMADOL may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction and other psychotropic substances, particularly alcohol.

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

Immune system disorders:

Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, Quincke's oedema) and anaphylaxis

Psychiatric disorders:

Rare: hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares. Psychic adverse reactions may occur following administration of TREMADOL 50 mg, tablet which vary individually in intensity and nature (depending on individual reactivity and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually decreased activity, occasionally increased) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders).

Abuse and dependence have been reports, as well as cases of withdrawal syndrome.

Symptoms of withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

Other withdrawal symptoms that have very rarely been reported including: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and other CNS disorders (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

Nervous system disorders:

- *Very common:* dizziness
- *Common:* headache, somnolence
- *Rare:* paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.

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).

- Unknown *frequency*: loss of consciousness, serotonin syndrome.

Metabolism and nutrition disorders:

- *Rare: change in appetite.*
- *Not known:* hypoglycaemia

Eye disorders:

Rare: miosis, blurred vision, mydriasis.

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

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.

Respiratory, thoracic and mediastinal disorders:

Rare: respiratory depression, dyspnoea

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly, respiratory depression may occur (see section 4.5).

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

Gastrointestinal disorders:

Very common: nausea

Common: constipation, dry mouth, vomiting

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

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.

Skin and subcutaneous tissue disorders:

Common: hyperhidrosis

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

Musculoskeletal and connective tissue disorders:

Rare: motorial weakness

Renal and urinary disorders:

Rare: micturition disorders (dysuria and urinary retention)

General disorders and abnormalities at the administration site:

Common: fatigue

Investigations:

Rare: increase in blood pressure

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk ratio of the medicinal product.

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.

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 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 formulation.

Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore, treatment of acute intoxication with TREMADOL 50 mg tablet with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: OTHER ANALGESICS OPIOIDS, ATC code: N02AX02

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and k opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect

of the product 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 to 1/6 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 studied in those trials included the treatment of post-operative pain (mainly abdominal surgery), post-dental surgery pain, or following fractures, burns and traumas as well as other painful conditions that may 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 (without exceeding the maximum dose of 400 mg per day) efficacy of tramadol was greater than that of placebo, and greater than or equal to paracetamol, nalbuphine, pethidine or low dose morphine. These 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

After a single oral administration of a dose of 50 to 100 mg, the bioavailability is between 70 and 90%.

After oral administration, repeated every 6 hours, 50 to 100 mg, the steady state is rapidly reached in about 36 hours and the bioavailability increases, exceeding 90%.

The serum peak after oral administration of 100 mg of tramadol is about 300 ng / ml (Cmax) and is reached after about 2 h (tmax).

Plasma protein binding is 20%, and the volume of distribution is high (3 to 41 / kg). Tramadol crosses the placental barrier and passes in very small quantities into breast milk (approximately 0.1% of the maternal dose administered).

The elimination half-life is between 5 and 7 h in healthy volunteers; 90% of tramadol is metabolized, mainly in the liver; One of the demethylated metabolites has an analgesic effect; its half-life is of the same order as that of tramadol.

Inhibition of one or both of the cytochromes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may alter the plasma concentration of tramadol or its active metabolites.

Tramadol and its metabolites are almost completely excreted via the renal route (95%). The remainder is eliminated in the faeces.

The pharmacokinetic of tramadol is only slightly affected by the age of the patient; In patients over 75 years of age, the half-life is slightly increased.

In patients with renal insufficiency, the clearance of tramadol is decreased in parallel with creatinine clearance; The half-life is on average 12 hours.

In hepatic insufficiency, the clearance of tramadol is decreased, depending on the severity of liver failure.

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multipleoral doses to subjects aged 1 year to 16 years are generally similar to those observed in adults after dose adjustment to body weight, but with a higher between-subject variability in patient under 8 years.

The pharmacokinetic profiles of tramadol and O-desmethyltramadol have been studied in children less than 1 year of age but have not been fully characterized. Data for this age group from clinical studies indicate that the formation rate of O-desmethyltramadol via cytochrome CYP2D6 increases continuously in the neonate to

adult levels of CYP2D6 activity are at about 1 year old. Additionally, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children younger than 1 year.

5.3. Preclinical safety data

After repeated oral and parenteral administration of tramadol for 6 to 26 weeks in rats and dogs and after oral administration for 12 months in dogs, no active substance-related changes were observed in haematological, biochemical and histological parameters.. Central neurological effects were observed only after high doses, considerably higher than therapeutic doses: agitation, salivation, convulsions and reduction in weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg, respectively, and dogs rectal doses of 20 mg/kg, without showing abnormal reactions.

In rats doses of tramadol greater than or equal to 50 mg/kg/day caused toxic effects in dams and increased neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male and female fertility was not affected.

In rabbits, maternotoxic have been reported at doses greater than or equal to 125 mg/kg as well as 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 hepatocellular adenomas in male (non-significant dose-dependent, increase from 15 mg/kg) and an increased incidence of pulmonary tumours in females of all treated groups (significant increase, but not dose- dependent).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Starch Glycolate (type A); Microcrystalline Cellulose, Mannitol; Magnesium Stearate; Colloidal Anhydrous Silica.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

No special storage conditions.

6.5 Nature and contents of container

PVC / ALU blister pack of 20 tablets.

6.6 Special precautions for disposal and other handling

Do not dispose of any medicine via wastewater or household waste.

Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.