SUMMARY OF PRODUCT CHARACTERIZATION (SMPC) FOR Tramadol 50mg Capsules

1. Name of the medicinal product Tramadol 50mg Capsules

2. Qualitative and quantitative composition

Each capsule contains 50 mg tramadol hydrochloride For the full list of

excipients, see section 6.1.

3. Pharmaceutical form Hard Gelatine Capsules.

4. Clinical particulars

4.1 Therapeutic indications Treatment of moderate to severe

pain in adults.

4.2 Posology and method of administration

Adults (17 years of age and over) For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of tramadol can be improved by initiating therapy with the following titration regimen: tramadol should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 20 days to reach 200 mg/day (50 mg q.i.d.). After titration, tramadol 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day. For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, tramadol 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day. Individualization of Dose Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Studies with tramadol in adults have shown that starting at the lowest possible dose and titrating upward will result in fewer discontinuations and increased tolerability.

• In all patients with creatinine clearance less than 30 mL/min, it is recommended that the dosing interval of tramadol be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, dialysis patients can receive their regular dose on the day of dialysis.

• The recommended dose for adult patients with cirrhosis is 50 mg every 12 hours.

• In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients over 75 years old, total dose should not exceed 300 mg/day.

4.3 Contraindications

Tramadol should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. tramadol is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol may worsen central nervous system and respiratory depression in these patients.

Seizure Risk Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range.

Concomitant use of tramadol increases the seizure risk in patients taking:

- Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine , promethazine, etc.), or 7
- Other opioids. Administration of tramadol may enhance the seizure risk in patients taking:
- MAO inhibitors (see also Use with MAO Inhibitors and Serotonin Re- Uptake Inhibitors),
- Neuroleptics, or other drugs that reduce the seizure threshold.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections) . tramadol overdose, naloxone administration may increase the risk of seizure. Suicide Risk

- Do not prescribe tramadol for patients who are suicidal or addiction-prone.

- Prescribe tramadol Tablets with caution for patients who are taking tranquilizers or antidepressant drug and patients who use alcohol in excess and who suffer from emotional disturbance or depression. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs (Risk of Overdosage).

Serotonin Syndrome Risk The development of a potentially life threatening serotonin syndrome may occur with the use of tramadol products, including tramadol, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs, and triptans, with drugs which impair metabolism of serotonin (including MAOIs), and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). This may occur within th e recommended dose. 8 Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Anaphylactoid Reactions Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur, it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens- Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol (se CONTRAINDICATIONS).

Respiratory Depression Administer tramadol cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see WARNINGS, Seizure Risk and OVERDOSAGE).

Interaction With Central Nervous System (CNS) Depressants tramadol should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. tramadol increases the risk of CNS and respiratory depression in these patients. Interactions with Alcohol and Drugs of Abuse Tramadol may be expected to have additive effects when used in conjunction with

alcohol, other opioids, or illicit drugs that cause central nervous system depression. IncreasedIntracranial Pressure or Head Trauma tramadol should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered 9 mental status in these patients if they are receiving tramadol (see WARNINGS, Respiratory Depression). Use in Ambulatory Patients tramadol may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly. Use With MAO Inhibitors and Serotonin Re- uptake Inhibitors Use tramadol with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

4.4 Special warnings and precaution for use

Renal Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1.

In patients with creatinine clearances of less than 30 mL/min, adjustment of the dosing regimen is recommended.

The total amount of tramadol and M1 removed during a 4- hour dialysis period is less than 7% of the administered dose. Hepatic Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and longer tramadol and M1 elimination half- lives (13 hrs. for tramadol and 19 hrs. for M1).

In cirrhotic patients, adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION).

Geriatric

Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs. 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years (see DOSAGE AND ADMINISTRATION).

Gender

The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of

tramadol.

Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35% higher area under the concentration-time curve compared to males. The clinical significance of this difference is unknown.

4.5 Drug Interactions

CYP2D6 and CYP3A4 inhibitors Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors (see CLINICAL PHARMACOLOGY, Pharmacokinetics), such as quinidine, fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), and ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol increasing the risk for serious adverse events including seizures and serotonin syndrome. Serotonergic Drugs There have been post marketing reports of serotonin syndrome with use of tramadol and SSRIs/SNRIs or MAOIs and α2-adrenergic blockers. Caution is advised when tramadol is co- administered with other drugs that may affect the serotonergic neurotransmitter systems, such as SSRIs, MAOIs, triptans, linezolid (an antibiotic which a reversible non-selective MAOI), lithium, or St. John's Wort. If concomitant treatment of tramadol with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient i s advised, particularly during treatment initiation and dose increases (see WARNINGS, Serotonin Syndrome). Triptans Based on the mechanism of action

of tramadol and the potential for serotonin syndrome, caution is advised when tramadol is co-administered with a triptan. If concomitant treatment of tramadol with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS, Serotonin Syndrome). 12 Use With Carbamazepine Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol and carbamazepine is not recommended. Use With Quinidine Tramadol is metabolized to M1 by CYP2D6. Quinidine is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism. Potential for Other Drugs to Affect Tramadol In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with tramadol may affect the metabolism of tramadol leading to altered tramadol exposure. Potential for Tramadol to Affect Other Drugs In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4- mediated metabolism of other drugs when tramadol is administered concomitantly at

therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals. Use With Cimetidine Concomitant administration of Tramadol with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

Therefore, no alteration of the tramadol dosage regimen is recommended. Use With Digoxin and Warfarin Post-marketing surveillance has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

4.6 Fertility, pregnancy and lactation

pregnancy

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. 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 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

Not known: hypoglycaemia

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: paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.

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 (usuallysuppression, 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, paresthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalization, derealization, 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

General disorders:

Common: fatigue

4.6 Over dose

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.

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 formulations.

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.

Overdose

Serotonin syndrome has also been reported.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, opioids, other opioids.

ATC Code: N02 AX02

Mechanism of action

CLINICAL PHARMACOLOGY

Pharmacodynamics

tramadol contains tramadol, a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially 1 antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours. Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

5.2 Pharmacokinetic properties Absorption

More than 90% of Tramadol 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 %.

Distribution

Tramadol has a high tissue affinity (V d,ß = 203 + 40 l). It has a plasma protein binding of about 20 %.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean Cmax of 280 to 208 mcg/L and Tmax of 1.6 to 2h.

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).

Biotransformation

In human tramadol is mainly metabolized by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only Odesmethyltramadol 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 t1/2,ß (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.

Elimination

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 + 4.9 h (tramadol) and 18.5 + 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 + 3.2 h and 16.9 + 3 h, in an extreme case 19.5 h and 43.2 h respectively.

Elimination half-life t1/2,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.

Linearity/non-linearity

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.

Pediatric 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 Odesmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of Odesmethyltramadol 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

Carcinogenesis, Mutagenesis, Impairment of Fertility A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice.

Mice were dosed orally up to 30 mg/kg (90 mg/m2 or 0.36 times the maximum daily human dosage of 246 mg/m2) for approximately two years, although the study was not done with the Maximum Tolerated Dose.

This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m2 , or 0.73 times the maximum daily human dosage). Tramadol was not mutagenic in the following assays:

Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats.

Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans. No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (300 mg/m2) in male rats and 75 mg/kg (450 mg/m2) in female rats. These dosages are

1.2 and 1.8 times the maximum daily human dosage of 246 mg/m2 , respectively. Pregnancy, Teratogenic Effects: Pregnancy Category C Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or 360 mg/m2), rats (≥25 mg/kg or 150 mg/m2) and rabbits (≥75

mg/kg or 900 mg/m2) at maternally toxic dosages, but was not teratogenic at these dose levels. These dosages on a mg/m2 basis are 1.4, ≥0.6, and ≥3.6 times the maximum daily human dosage (246 mg/m2) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420 mg/m2), rats (up to 80 mg/kg or 480 mg/m2) or rabbits (up to 300 mg/kg or 3600 mg/m2) treated with tramadol by various routes.

Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels.

Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver.

Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg (3600 mg/m2), a dose that would cause extreme maternal toxicity in the rabbit.

The dosages listed for mouse, rat 14 and rabbit are 1.7, 1.9 and 14.6 times the maximum daily human dosage (246 mg/m2), respectively. Non-teratogenic Effects Tramadol was evaluated in peri- and post-natal studies in rats.

Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m2 or 1.2 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m2 or 1.9 and higher the maximum daily human dose).

6 Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose

Sodium starch glycolate

Colloidal anhydrous silica

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

White transparent PVC/Aluminium Blister Strip containing 10 capsules

6.6 Special precautions for disposal and other handling

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

7 Marketing authorization holder

Manufactured and distributed by

Daily Sun Pharmaceutical Company Limited

Plot 3 & 4, Tomori Industrial Estate, Off Idi-Iroko Road, Ota, Ogun State, Nigeria.

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