1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

----(Enclosed)----

Summary of Product Characteristics

1. Name of the medicinal product

Dolburg 50

2. Qualitative and quantitative composition

Each hard gelatin capsule contains :

Tramadol Hydrochloride BP	50 mg
Excipients	q.s.

Approved colour used in empty capsule shells.

3. Pharmaceutical form

Hard Gelatin Capsule

4. Clinical particulars

4.1 Therapeutic indications

Management (treatment and prevention) 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 individual's response to the analgesic action of Tramadol. Tramadol should not be used for the treatment of minor pain.
Adults and children aged 12 years and over

Oral administration

Moderate pain: Initial dose of 50mg, followed by 50mg or 100mg 4-6 hourly.

Moderately severe pain: Initial dose of 50mg, followed by 50mg or 100mg 4-6 hourly. A total oral daily dose of more than 400mg per day must not be exceeded.

Elderly: The usual dosages may be used except in patients up to 75 years of age and over, a downward adjustment of the dose and/or prolongation of the interval between doses are recommended.

4.3 Contraindications

Tramadol is contraindicated in known hypersensitivity to tramadol hydrochloride or opioids, in acute intoxication with alcohol, hypnotics, analgesics or psychotropic medicines. It should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal. Tramadol must not be used for narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Cases of dependence and abuse have been reported rarely.

Tramadol should be used with caution in patients with head injury, increases intracranial pressure, severe impairment of hepatic and renal function and tramadol is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects. Combination of mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. 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 new-born infants 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.

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 following side-effects have been reported:

Gastrointestinal system: Nausea, vomiting, dry mouth, heartburn, constipation

Central nervous system and Psychiatric: Fatigue, sedation and coma, seizures and respiratory depression.

4.9 Overdose

Symptoms of overdose are typical of other opioid analgesics and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Tramadol is a centrally acting analgesic effective for moderate to severe acute and chronic pains. Tramadol consists of two enantiomers. The (+)- isomer is predominantly active as an opiate as well. The metabolite has a six times stronger affinity for the μ-receptor in vivo than tramadol. In vitro this affinity is 170 times stronger. The (-) - isomer acts as an inhibitor of the re-uptake of noradrenaline and potentiates the analgesic action of the (+)-isomer. The contribution of the stimulation of the serotonin release is considered low.

5.2 Pharmacokinetic properties

Tramadol is absorbed after oral administration. The absolute biological availability is 60-95% (on average 72 %). Maximum serum concentrations are reached after approximately 1 hour. Plasma protein binding amounts to 20%. Tramadol passes the blood-brain barrier and the placenta.

The excretion of tramadol or its metabolites in human milk is small (0.1%).

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, nonsignificant 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

Lactose, Starch, Purified Talc, Colloidal Anhydrous Silica, Methyl HydroxyBenzoate, Propyl HydroxyBenzoate, Sodium Lauryl Sulphate, Croscarmellose sodium, Magnesium Stearate, Microcrystalline Cellulose. EHG Capsule (4) Metallic Dark Green/ Metallic Light Green.

6.2 Incompatibilities

None known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 30°C.

Keep out of the reach of children.

6.5 Nature and contents of container

Alu-PVC Blister Pack of 10X10 Capsules in a carton box along with insert.

6.6 Special precautions for disposal and other handling

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

7. Applicant/Manufacturer

Rhydburg Pharmaceuticals Ltd.

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