Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

BioDol 50mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50mg tramadol hydrochloride capsule contains: 50mg tramadol hydrochloride
Excipients: Each capsule contains 70mg of lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard.

Olive/yellow hard capsules imprinted “TRM” on the capsules cap and “50” on the capsules body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

For oral administration.

As with all analgesic drugs, the dose of tramadol should be adjusted according to the severity of the pain and the clinical response of the individual patient. Treatment periods should be short and intermittent as dependence can occur with tramadol. The benefits of continued use should be reviewed in order to ensure that they outweigh the risks of dependence (see Special Warnings and Precautions for Use and Undesirable Effects section).

Adults and Children Aged 12 Years and Over

Acute pain
An initial dose of 100mg is usually necessary. This can be followed by doses of 50 or 100 mg not more frequently than 4 hourly, and duration of therapy should be matched to clinical need.

Pain associated with chronic conditions
Use an initial dose of 50mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (See Section 4.4, *Special Warnings and Precautions for Use*).

A total daily oral dose of 400mg is not usually required or recommended.

Elderly
The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half-life of tramadol was increased by 17% following oral administration.

Renal impairment/renal dialysis
The elimination of tramadol may be prolonged. The usual initial dosage should be used. For patients with creatinine clearance < 30ml/min., the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with creatinine clearance < 10ml/min (see 4.3 Contraindications).

Hepatic impairment
The elimination of tramadol may be prolonged. The usual initial dosage should be used but in moderate hepatic impairment the dosage interval should be increased to 12 hours. Tramadol is not recommended in severe hepatic impairment (see 4.3 Contraindications).

Children under 12 years
Not recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Tramadol should not be administered to patients who have previously demonstrated hypersensitivity to it or in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs, or in patients suffering from uncontrolled epilepsy. Tramadol must not be used for narcotic withdrawal treatment. In common with other opioid analgesics it should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5) or to patients with severely impaired liver function or creatinine clearance < 10ml/min.

4.4 Special warnings and precautions for use

Warnings
At therapeutic doses, tramadol has the potential to cause physical dependence and withdrawal symptoms. Rarely, cases of dependence and abuse have been reported.Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop.

At therapeutic doses, withdrawal symptoms have been reported at a reporting frequency of 1 in 8,000. Reports of dependence and abuse have been less frequent. Because of this potential, the clinical need for continued analgesic treatment should be reviewed regularly.

In patients with a tendency to drug abuse or dependence, treatment should be for short periods 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.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400mg). 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 - *Interactions with other Medicaments and other Forms of Interactions*).

Precautions
Tramadol should be used with caution in patients with head injury, increased intracranial pressure, opioid- dependent patients, disorders of the respiratory centre or function and in patients prone to convulsive disorders or in shock.

Caution should be exercised in patients with hepatic or renal insufficiency (creatinine clearance < 30 ml/min). The dosing interval may need to be prolonged (see 4.2 Posology and method of administration and 4.3 Contraindications).

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, 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. At therapeutic doses, respiratory depression has infrequently been reported.

In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intraoperative recall. Until further information is available use of tramadol during light planes of general anaesthesia should be avoided.

Caution should be exercised in patients with a previous history of hypersensitivity to other opiates, and in patients with decreased level of consciousness of uncertain origin.

Excipients
The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of tramadol with other centrally acting drugs including alcohol may potentiate CNS depressant effect. Tramadol should not be combined with MAO inhibitors (see section 4.3 Contraindications).

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 Tramadol.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR and ecchymoses in some patients.

Tramadol may increase the potential for both selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions (See Sections 4.4 - *Special Warnings and Special Precautions for Use* and 5.2 - *Pharmacokinetic Properties*).

Tramadol may also increase the potential for anti-psychotics and other seizure threshold lowering drugs to cause convulsions.

Simultaneous administration of carbamazepine (enzyme inducer) markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

There is a theoretical possibility that tramadol could interact with lithium due to their respective mechanisms of action.

The combination of mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not recommended because it is theoretically possible that the analgesic effect of a pure agonist is attenuated under these circumstances.

Isolated cases of serotonergic syndrome have been reported with the therapeutic use of tramadol in combination with other serotonergic agents such as selective serotonin re-uptake inhibitors (SSRIs) or with MAO inhibitors. Serotonergic syndrome can be manifested by symptoms such as confusion, agitation, restlessness, fever sweat, ataxia, hyperreflexia, myoclonia and diarrhoea. The withdrawal of the serotonergic agent produces a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Administration of tramadol together with carbamazepine results in markedly decreased serum concentrations of tramadol which may reduce analgesic effectiveness and shorten the duration of action.

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 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of tramadol in pregnant women. 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. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Tramadol should not be used during pregnancy.

Lactation
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. Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of the dose given to the mother. Tramadol should not be administered during breast feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions, Tramadol may cause drowsiness and dizziness and this effect may be potentiated by alcohol and other and psychotropic substances (CNS depressants)and therefore may impair the reactions of drivers and machine operators. Ambulant patients should be warned not to drive or operate machinery if affected.

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

Cardiovascular disorders:

uncommon: cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

rare: bradycardia, increase in blood pressure

Nervous system disorders:

very common: dizziness

common: headache, somnolence

rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.

not known: speech disorders

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

Epileptiform 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, 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). Dependence may occur.

Eye disorders:

rare: blurred vision

not known: mydriasis

Respiratory disorders:

*rare :*dyspnoea

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

Gastrointestinal disorders:

very common: nausea

common: vomiting, constipation, dry mouth

uncommon : retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea

Skin and subcutaneous disorders:

common : sweating

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

Musculoskeletal 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 (difficulty in passing urine, dysuria and urinary retention)

General disorders:

common : fatigue

rare : allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; Symptoms of withdrawal reactions, 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, personalisation, derealisation, paranoia).

4.9 Overdose

In principle, on intoxication with tramadol Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, cardiovascular collapse, sedation and consciousness disorders up to coma, seizures and respiratory depression up to respiratory arrest.

Treatment
The general emergency measures apply.Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression. In animal experiments naloxone had no effect on convulsions: fits can be controlled with diazepam 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.

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

ATC Code: N02A X02
Tramadol is a centrally acting analgesic with two mechanisms of action. It is a non-selective pure agonist at opioid receptors with a higher affinity for μ receptors. It is also an inhibitor of neuronal reuptake of noradrenaline and serotonin.

5.2 Pharmacokinetic properties

Tramadol is almost completely absorbed following oral administration. The mean absolute bioavailability is approximately 70% due to low first-pass effect. The bioavailability is independent of concomitant intake of food.

Therapeutic serum levels are considered to be dose related and are in the range of 100 to 300 ng/ml with considerable inter-individual variability. Tramadol has a high tissue affinity with a volume of distribution of about 203 litres. Protein binding is about 20%.

Tramadol crosses the blood-brain and placental barriers. Tramadol is metabolised to a high extent after oral administration. The main metabolic pathway appears to be by means of N- and O-demethylation and glucuronidation or sulfation in the liver. The O-desmethyl metabolite has been shown to have analgesic effects in animal experiments. O-desmethylation is catalyzed by the polymorphic enzyme CYP2D6.

About 5-10% of the caucasian population are slow metabolisers and have reduced activity of the enzyme CYP2D6. The serum concentration of tramadol is higher in individuals with slow metabolism compared to those with faster metabolism, while the concentration of O-desmethyl tramadol is lower.

The inhibition of one or both types of the iso-enzymes CYP3A4 (eg. ketoconazole, erythromycin) and CYP2D6 (fluoxetine, paroxetine, quinidine, ritonavir) involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or it's active metabolite. The same applies for enzyme inducers (eg. rifampicin, fenytoin). Up to now, no clinically relevant interactions have been reported.

About 30% of the dose is excreted unchanged in the urine while 60% of the dose is excreted as metabolites.

The elimination half-life of tramadol is approximately 6 hours. In renal or hepatic insufficiency, a slight prolongation of the half-life can be expected. In severe insufficiency (eg. cirrhosis of the liver, creatinine clearance < 5 ml/min), a 2-3 fold prolongation of the half-life can be expected. In elderly patients (> 75 years of age), the elimination half-life may be prolonged by a factor of 1.4.

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)

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential. Studies in rats and rabbits have revealed no teratogenic effects. However, embryotoxicity was shown in the form of delayed ossification. Fertility reproductive performance and development of offspring were unaffected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose (E460(i))
Croscarmellose sodium (E466)
Magnesium stearate (E572)
Capsule shell excipients :

Body:	Erythrosin (E127)
	Titanium dioxide, (E171)
	Yellow iron oxide (E172)
	Gelatin
Cap:	Indigo carmine (E132)
	Titanium dioxide (E171)
	Black iron oxide (E172)
	Yellow iron oxide (E172)
	Gelatin
Ink:	Opacode Black S-1-27794 (Colorcon)
	Shellac Glaze
	Black Iron Oxide JPE (E172)
	Propylene Glycol (E1520)
	N-Butyl Alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package; in order to protect from moisture.

6.5 Nature and contents of container

Al/PVC/PVdC blister.
Blister packs of 10, 20, 30 50, 60 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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