# Magadol

(Tramadol Hydrochloride B.P. Ph. Eur.)

# میگاڈول

(ٹرامادول ہائیڈروکلورائیڈ بی۔پی۔)

**Composition:**
**Capsule:** Each capsule 50mg of tramadol hydrochloride Ph. Eur.
The chemical designation is (1 RS 2 RS)-2-(dimethylaminomethyl)-1-(m-methoxphenyl)-cyclohexanol-hydrochloride.

**Pharmacodynamics:**
Opioid activity (weak mu receptor agonist i.e. affinity for mu receptor is 6000 times less than morphine ) provides analgesic as morphine with comparatively less side effects.

Non opioid activity (mono-aminergic action i.e. inhibition of noradrenaline and serotonin)

**Pharmacokinetic properties:**
In human about 90% of **Magadol** (Tramadol hydrochloride) is absorbed after oral administration, shows a bioavailability of 68 ± 13% for capsules.

Peak serum concentrations are achieved about 2 h after administration of capsules.

**Magadol** (Tramadol hydrochloride) has a high tissue affinity. It has a plasma protein binding ratio of about 20%.

**Magadol** (Tramadol hydrochloride) and its metabolites are almost completely excreted via the kidneys. Elimination half-life $t_{1/2}$ is approximately 6hrs. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4. In humans tramadol is mainly metabolised by means of N. and O-demethylation and conjugation of the O-demethylation products with glucuronic acid.

Only O-desmethyltramadol is pharmacologically active.

**Indications:**
Moderate to severe pain.

**Contraindications:**
**Magadol** (Tramadol hydrochloride) must not be administered in known hypersensitivity towards tramadol or any of the excipients or in acute intoxication with alcohol, hypnotics, analgesics or other CNS acting drugs. **Magadol** (Tramadol hydrochloride) must not be used for narcotic withdrawal treatment. **Magadol** (Tramadol hydrochloride) must be used with special "care in opioid dependence, reduced level of consciousness of unclear origin, disorders of the respiratory centre or function, increased intracranial pressure. **Magadol** (Tramadol hydrochloride) must not be used in patients with epilepsy not adequately controlled by treatment. **Magadol** (Tramadol hydrochloride) must not be used in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see "Interactions").

**Warnings and Precautions for Use:**
**Magadol** (Tramadol hydrochloride) may only be used after careful consideration of the benefit/risk ratio and relevant precautions in - dependence on opioids;
- Consciousness disorders of uncertain origin, shock.
- disorders of the respiratory centre or function.
- increased intracranial pressure due to head injuries or brain diseases.

If patients sensitive to opiates the medicinal product should only be used with caution. Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400mg). In addition, tramadol may increase the seizure risk in patients taking other medication that lowers the seizure threshold (see "interaction"). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances. Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment with **Magadol** (Tramadol hydrochloride) should only be carried out for short periods under strict medical supervision.

**Magadol** (Tramadol hydrochloride) is not suitable as a substitute in opioid-dependent patients. Although Tramadol is an opiate agonist, it cannot suppress morphine withdrawal symptoms.

**Use in pregnancy and lactation**
There is inadequate evidence available on safety of tramadol in human pregnancy. Therefore tramadol should not be used in pregnancy. Tramadol passes the placental barrier and withdrawal symptoms may occur in the neonate due to habituation. When given before or during birth, tramadol does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant.
Only very small quantities of tramadol (approx. 0.1% of an i.v. dose) are excreted in the breast-milk. Therefore tramadol should not be used during lactation. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

**Side-effects:**
Frequently nausea and dizziness have been reported.
Occasionally vomiting, constipation, sweating, dry mouth, headache, and dizziness my occur,
In rare cases there may be effects on cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially on intravenous administration and in patients who are physically stressed. Gastrointestinal irritation (a feeling of pressure the stomach, bloating) and dermal reactions (e.g. pruritus, rash, urticaria) may occur in rare cases.

In very rare cases motorial weakness, changes in appetite, blurred vision and micturition disorders (difficulty in passing urine and urinary retention) have been observed. Also in very rare cases various psychic side effects may occure following administration of **Magadol** (Tramadol hydrochloride) which vary individually in intensity and nature (depending on personality and duration of medication). 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 behavior, perception disorders). Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis have also been reported in very rare cases.

Worsening of asthma has also been reported in very rare cases, though a causal relationship has not been established.

Very rarely epileptiform convulsions have been reported. They occured mainly after administration of high doses of tramadol or after concomitant treatment with drugs which can lower the seizure threshold of themselves induce cerebral convulsions (e.g. antidepressants or neuroleptics).

Increase in blood pressure and bradycardia have been reported in very rare cases. Respiratory depression has been reported. If the recommended doses are considereably exceeded and other centrally depressant substances are administered concomitantly, respiratory depression may occur. Dependence may develop. Symptoms or withdrawal reactions, similar to those occuring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

in a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol. Other symptoms have rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations paraesthesia, tinnitus, and unusual CNS symptoms.

**Note for road users and machine operators**
Even when used according to instructions. **Magadol** (Tramadol hydrochloride) may affect reactions to such an extent that road safety, the operation of machinery and working without a firm hold may be impaired. This applies particularly when starting treatment, switching from other medicinal products in conjunction with other centrally acting drugs and in particularly, with alcohol.

**Interaction with Other Drugs:**
On premedication with MAO inhibitors in the last 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system and respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors and **Magadol** (Tramadol hydrochloride) cannot be excluded.

Concomitant administration of **Magadol** (Tramadol hydrochloride) with other centrally depressant substances including alcohol may potentiate the CNS effects. In isolated cases there have been reports of serotonin syndrome in a a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicinal products such as selective serotonin re uptake inhibitors (SSRIs) or with MAO inhibitors. Sign of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhea, Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms. Tramadol may induce convulsions and increase the potential of selective serotonin re-uptake inhibitors, tricyclic anti-depressants, neuroleptics and other seizure threshold lowering drugs to cause convulsions.

The results of pharmacokinetics studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. Simultaneously or previous administration of carbamazepine (enzyme inducer), may reduce the analgesic effect and shorten the duration of action. The combination with mixed agonist/antagonists (e.g. Buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Other drugs known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (O-demethylation) possibly also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied. **Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. Warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.**

**Principal Incompatibilities:**
None

**Application and Dosage:**
The dosage should be adjusted to the intensity of pain. Unless otherwise prescribed.

Capsules: should be taken as follows with or without meals:
Single dose for adults and adolescents over 12 years of age:

1-2 capsules (50-100 mg. tramadol hydrochloride) to be taken with a little. If pain relief is unsatisfactory, a further Magadol (Tramadol hydrochloride B.P.) capsule may be taken after about 30-60 minutes. If in severe pain the analgesic demnand is likely to be higher, the higher dose (2 capsules) can be given as initial dose.

Daily doses of 400mg tramadol are usually sufficient. However, in the treatment of tumour pain and severe postoperative pain much higher daily doses have been used.

**Children:** On account of the dosage strength. **Magadol** (Tramadol hydrochloride) are not recommended for children below the age of 12 years.

**Geriatric Patients:** In old patients (above 75 years of age) elimination may be prolonged. In this case the dosage interval should be prolonged according to individual requirements.

**Renal or Hepatic Insufficiency:**
In patients with impaired renal or hepatic function the duration of action of **Magadol** (Tramadol hydrochloride) may be prolonged. If pain recurs, the dosage interval should be extended.

**Duration of Treatment:**
**Magadol** (Tramadol hydrochloride) must not be given for longer than therapeutically absolute necessary. If long-term pain treatment is necessary, checks should be carried out at regular and brief intervals (if necessary with breaks in treatment) as to whether and in what doses further treatment with **Magadol** (Tramadol hydrochloride) is necessary.

**Overdosage:**
Symptoms: In principal, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected, in particular miosis, vomiting, cardiovascular collapse, reduced level of consciousness up to coma, convulsions and respiratory depression upto respiratory arrest:

**Treatment:** The general emergency measures to keep open the respiratory tract (aspiration!) maintenance of respiration and circulation depending on the symptoms apply. An Antidote for respiratory depression is naloxone. In animal studies naloxone had no effect on convulsions. In such cases diazepam should be given i.v.

**Stability:**
**Magadol** (Tramadol hydrochloride) should not be used after the expiry date printed on the packing.

**Instructions:**
Store at room temperature (15-25°C). Protect from moisture and sunlight. Keep out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

**ہدایات:**
دوا کو (15 - 25°C) درجہ حرارت پر نمی اور دُھوپ سے محفوظ رکھیں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ دوا صرف مستند ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔

**PACKAGE QUANTITIES**
Magadol Tablets : Box of 1 x 10's blister packed capsules.

Marketed by:
ORGANIC Pharmaceuticals

**Manufactured by:**
SAFE Pharmaceuticals (Pvt.) Ltd.
C-I-20, Sector 6-B, North Karachi
Industrial Area, Karachi-Pakistan.
www.safepharmaceutical.com

PNAC CB 001 QMS | TÜV AUSTRIA | UKAS 014
ISO 9001: 2008 CERTIFIED