SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Marol 150mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Marol tablets are prolonged release tablet containing 150 mg of Tramadol hydrochloride.

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Marol 150 mg tablets are off white, capsule shaped tablets, 14.3 mm long

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

Route of Administration

Oral use

Posology

The dose should be adjusted to the severity of the pain and the individual clinical response of the patient.

Unless otherwise prescribed, Marol tablets should be given as follows:

Adults and adolescents older than 12 years:

The usual initial dose is one 100mg tablet, twice daily, in the morning and evening.

Dependent upon the needs of the patient, subsequent doses may be administered earlier than 12 hours, but must not be administered earlier than 8 hours after the previous dose.

If the painkilling is insufficient, the dose may be increased to:

one 150mg tablet, twice daily or

one 200mg tablet, twice daily.

Marol tablets should be swallowed completely, without breaking or chewing, independent of meals, with sufficient liquid.

The dose used should be the lowest dose that provides pain relief. A daily dose of 400 mg of tramadol is usually sufficient, except in special clinical circumstances.

Under no circumstances should Marol tablets be used for longer than absolutely necessary.
If long-term pain treatment with Marol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether, and to what extent, further treatment is necessary.

Children

Marol Tablets are not suitable for children under the age of 12 years.

Elderly

As a rule adjustment of the dose, in elderly patients (up to 75 years) without any clinical manifestations of hepatic or renal impairment, is not necessary. In older patients (above 75 years) the elimination may be delayed. In which case the dose interval should be prolonged.

Renal impairment, dialysis and hepatic impairment

In patients with serious renal or hepatic impairment the use of Marol tablets are not recommended. In moderate cases, an adjustment of the dosage interval may be considered.

4.3 Contraindications

Marol tablets should not be used in:

- hypersensitivity to tramadol, or any excipients in the tablet (see section 6.1),

- in acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic drugs.

- in patients receiving MAO-inhibitors, or within 2 weeks of their withdrawal.

Marol tablets should not be used for narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Marol Tablets should be used with caution in patients dependent on opioids, patients suffering head injuries, shock, decreased level of consciousness of unknown origin, disturbances of the respiratory centre or function, or increased intracranial pressure.

In patients sensitive for opioids the medicine should be used cautiously.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400 mg). The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold. (see section 4.5). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons.

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 should be for short periods under strict medical supervision.

Tramadol is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol / MAO - inhibitors

Marol tablets should not be combined with MAO-inhibitors (see section 4.3).

Tramadol / Other centrally acting active substances

In concomitant use of Marol tablets and other centrally acting drugs, including alcohol, a potentiation of CNS effects should be taken into consideration (See section 4.8).

Tramadol / Enzyme inhibitor / inducer

The results of pharmacokinetic research, so far, showed that no interactions need to be expected in concomitant or prior use of cimetidine (enzyme inhibitor). The concomitant or prior use of carbamazepine (enzyme inducer) may reduce the analgesic effectiveness and shorten the duration of the action.

Tramadol / Mixed opioid agonists / antagonists

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.

Tramadol / Seizure threshold lowering drugs

Tramadol may induce convulsions and may increase the potential for selective serotonin re-uptake inhibitors, tricyclic antidepressants, anti-psychotics and other seizure threshold lowering drugs to cause convulsions.

Tramadol / Serotonergic agents

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). Serotonergic syndrome can be manifested by symptoms such as confusion, restlessness, fever, sweating, ataxia, hyperreflexia, myoclonia and diarrhoea. Withdrawal of the serotonergic agent produces a rapid improvement. It depends on the nature and severity of symptoms whether medicinal treatment is to be considered.

Tramadol / Coumarin derivatives

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 / CYP3A4 Inhibitors

Other medicinal products with a known inhibiting effect on CYP3A4, such as ketoconazole and erythromycin, could inhibit the metabolism of tramadol (N-demethylation) and probably also the metabolism of the active O-demethyl-metabolite. The clinical relevancy of this interaction has not been investigated. (See section 4.8).

4.6 Pregnancy and lactation

Animal tests with very large concentrations of tramadol showed effects on the development of the organs, bone formation and mortality of the neonate. Teratogenic effects have not been found. Tramadol passes the placenta; insufficient data are available to assess the safety of tramadol in pregnant women. Therefore Marol tablets should not be used during pregnancy.

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.
When breastfeeding about 0.1 % of the tramadol dose administered is excreted in milk. Administration of Marol Tablets is not advised while breastfeeding. In case of a once only administration of tramadol it is usually not required to discontinue breastfeeding.

4.7 Effects on ability to drive and use machines

Marol tablets may cause drowsiness and patients should be warned not to drive or use machinery if affected... This is especially applicable in combination with other psychotropic drugs.

4.8 Undesirable effects

The most commonly reported adverse drug reactions are nausea and dizziness, both occurring in more than 10% of patients.

Cardiac disorders*:*

Uncommon (>= 0.1 % - < 1%): 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.

Rare (>= 0.01 % - <0.1%): bradycardia, increase in blood pressure.

Nervous system disorders*:*

Very common (>= 10%): dizziness

Common (>= - 1 -10%): headache, drowsiness

Rare>= 0.01 % - < 0.1%): changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions.
If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section) respiratory depression may occur.

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with drugs which can lower the seizure threshold or themselves induce cerebral convulsions (see sections 4.4 and 4.5)

Psychiatric disorders*:*

Rare (>= 0.01 % - 0.1%): hallucinations, confusion, sleep disturbances and nightmares. Psychic side-effects may 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 behaviour, perception disorders).

Eye disorders:

Rare (>= 0.01 % - <0.1%): blurred vision

Respiratory disorders:

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

Gastrointestinal disorders*:*

Very common (>= 10%): nausea

Common (>= 1% -10%): vomiting, constipation, dry mouth.

Uncommon (>= 0.1 % - <1%): Retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating).

Skin and subcutaneous tissue disorders:

Common (>= 1 % - 10%): sweating

Uncommon (>= 0.1 % - <1%): dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal disorders:

Rare (>= 0.01 % - < 0.1%): motorial weakness

Hepato-biliary disorders:

In a few isolated cases (<= 0.01 %) an increase in liver enzyme values has been reported after use of tramadol.
Renal and urinary system disorders:

Rare (>= 0.01 % - < 0.1%): micturition disorders (difficulty in passing urine and urinary retention).

Immune system disorders:

Rare (>= 0.01 % - <0.1%): Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis;

General disorders:

Symptoms which occur on withdrawal, identical to withdrawal symptoms in opioids, may be: agitation, anxiety, nervousness, sleep disorders, hyperkinesia, tremor and gastro intestinal symptoms.

4.9 Overdose

Symptoms

In tramadol intoxication, in principle, the same symptoms occur as for all other central acting analgesics (opioids). In particular, these include miosis, vomiting, cardiovascular collapse, narrowing of consciousness leading to coma, convulsions, respiratory depression leading to respiratory failure.

Treatment

General emergency measures are applicable. Maintenance of the airway (aspiration), maintenance of respiration and cardiovascular circulation depending on the symptoms. Emptying of the stomach by means of vomiting (patient to be conscious) or by means of pumping the stomach. The antidote for respiratory depression is

nalaxone. In animal tests naloxone proved to be ineffective against convulsions. In that case diazepam should be administered intravenously.

Tramadol is only minimally removed from plasma using haemodialysis, haemofiltration or haemoperfusion. Therefore treatment of acute overdose of tramadol using haemodialysis or haemofiltration alone is not a suitable way of detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code N 02 AX 02: Pharmacotherapeutic group: Analgesics, other opioids

Tramadol is a centrally acting opioid analgesic. It is a non-selective, complete agonist of μ-, δ- and κ-opioid receptors with a higher affinity for μ-receptors. Other mechanisms contributing to the analgesic effect are the inhibition of the neural noradrenalin reuptake and an enhanced release of serotonin.

Tramadol has an antitussive action. Contrary to morphine tramadol does not suppress respiration in analgetic doses over a large range. In addition gastrointestinal motility is not influenced. The action on the cardiovascular system seems too minor. The potency of tramadol is reported to be 1/10 to 1/6 of morphine.

5.2 Pharmacokinetic properties

More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of concomitant intake of food.

The difference between absorbed and non-metabolised available tramadol is probably due to low first-pass effect. The first pass-effect after oral administration is a maximum of 30%.

Tramadol has a high tissue affinity ($V_{d,\beta}$ = 203 ± 40 l). Protein binding is about 20%.

After administration of tramadol 100mg prolonged release tablets the maximum peak plasma concentration C_{max} 141 ± 40 ng/ml is reached after 4.9 hours. After administration of tramadol 200mg prolonged release tablets a C_{max} 260 ± 62 ng/ml is reached after 4.8 hours.

Tramadol passes the blood-brain and placenta barrier. Very small amounts of the substance and its O-demethyl derivative are found in the breast-milk (0.1% and 0.02% respectively of the applied dose).

Elimination of half-life t½βis approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of 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. 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 t½β (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 cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite. The clinical consequences of any such interactions are not known.

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.

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.

5.3 Preclinical safety data

In repeated oral and parenteral administration of tramadol during 6 to 26 weeks to rats and dogs, as also during 12 months to dogs, there are no indications for changes caused by the substance in haematological, clinical-chemical and histological experiments. Only after high doses, far above the therapeutic doses, central symptoms occurred: restlessness, salivation, convulsion, reduced increase in weight. Rats and dogs tolerate the oral dose of 20 mg/kg resp 10 mg/kg bodyweight, dogs also tolerate 20 mg/kg bodyweight, rectally administered.

Tramadol doses as from 50 mg/kg/day cause intoxication of the mother, in rats, and result in an increased mortality in new born rats. In young rats development disorders occurred as ossification disturbances, delayed opening of the vagina and eyes. The fertility of male rats was not influenced.
However the percentage of females with young reduced after high dosages (as of 50 mg/kg/day).
In rabbits, toxic effects occurred as of 125 mg/kg in the mother and skeletal anomalies in the offspring.
In some *in-vitro* test systems there is report on mutagenic effects. In *in-vivo* experiments there was no indication for mutagenic effects.On the basis of the knowledge available up till now it is unclear whether tramadol possesses mutagenic potential.

Experiments have been performed on rats and mice with regard to the tumourigenic potential of tramadol. From tests in rats it could not be shown that the substance increases the chance of tumours.
In tests in mice an increased incidence of liver - cell adenomas in males (depending on the dose, with an insignificant increase as of 15 mg/kg) and an increased chance of lung tumours in females in all dose selections (significant, but not dose dependent) was found.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate (E341),

Hydroxypropylcellulose (E463),

Colloidal anhydrous silica (E551),

Magnesium stearate (E470b).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Al / clear PVC blisters in carton boxes in packs of 10, 20, 30, 50, 60, 90, 100, 120, and 180 tablets.

Al / opaque PVC blisters in carton boxes in packs of 10, 20, 30, 50, 60, 90, 100, 120, and 180 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)