MAROL 100MG PROLONGED-RELEASE TABLETS (PL 20117/0045)  
MAROL 150MG PROLONGED-RELEASE TABLETS (PL 20117/0046)  
MAROL 200MG PROLONGED-RELEASE TABLETS (PL 20117/0047)  

**UKPAR**

**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>10</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td>11</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>12</td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td>27</td>
</tr>
<tr>
<td>Labelling</td>
<td>29</td>
</tr>
</tbody>
</table>
LAY SUMMARY

The MHRA granted Morningside Healthcare Limited Marketing Authorisations (licences) for the medicinal product Marol 100mg, 150mg and 200mg Prolonged-Release Tablets on 22\(^{nd}\) February 2008. These products, to be available by prescription-only (POM), contain tramadol hydrochloride and are used for the treatment of moderate to severe pain.

The active ingredient tramadol hydrochloride is a centrally acting opioid analgesic, i.e. a pain killer that acts on pain centres in the brain.

These applications are duplicates of previously granted applications for Mabron 100mg, 150mg and 200mg Prolonged-Release Tablets (PL 20117/0003-0005), which were granted to Morningside Healthcare Limited in April 2006.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Marol 100mg, 150mg and 200mg Prolonged-Release Tablets outweigh the risks, hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 8
Clinical assessment Page 9
Overall conclusions and risk benefit assessment Page 10
INTRODUCTION

The UK granted marketing authorisations for the medicinal products Marol 100mg, 150mg and 200mg Prolonged-Release Tablets (PL 20117/0045-7) to Morningside Healthcare Limited on 22nd February 2008. The products are available as prescription-only medicines (POM).

The applications were submitted as simple abridged applications according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Mabron 100mg, 150mg and 200mg Prolonged-Release Tablets (PL 20117/0003-0005), which were granted to Morningside Healthcare Limited in April 2006.

No new data were submitted nor were necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products. For more information, the public assessment report for the cross-reference products Mabron 100mg, 150mg and 200mg Prolonged-Release Tablets is available on the MHRA website.

The active ingredient tramadol hydrochloride is a centrally acting opioid analgesic
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 20117/0045-7
PROPRIETARY NAME: Marol 100, 150 and 200mg Prolonged-Release Tablets
ACTIVE(S): Tramadol hydrochloride
COMPANY NAME: Morningside Healthcare Limited
LEGAL STATUS: POM

1. INTRODUCTION
These are simple, piggy back applications for Marol 100, 150 and 200mg Prolonged-Release Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Morningside Healthcare Limited, 115 Narborough Road, Leicester, LE3 0PA, UK.

The applications cross-refer to Mabron 100mg, 150mg and 200mg Prolonged-Release Tablets (PL 20117/0003-0005), which were granted to Morningside Healthcare Limited in April 2006.

The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)
The proposed names of the products are Marol 100, 150 and 200mg Prolonged-Release Tablets. The products have been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The products contain tramadol hydrochloride, equivalent to 100, 150 or 200mg. They are to be stored in either (i) an aluminium/clear polyvinylchloride blister strip or (ii) an aluminium/opaque polyvinylchloride blister strip in pack sizes of 10, 20, 30, 50, 60, 90, 100, 120 and 180 tablets. The applicant has stated that not all proposed packs are intended for marketing and that mock-ups of packaging will be submitted for approval before marketing any pack sizes.

The proposed shelf-life (36 months) and storage conditions (Do not store above 25°C) are consistent with the details registered for the cross-reference products.

2.3 Legal status
On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Morningside Healthcare Limited, 115 Narborough Road, Leicester, LE3 0PA, UK

The qualified person responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.
2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
No materials of animal or human origin are included in these products. This is consistent with the cross reference product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the products is identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summaries are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/CARTON

PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Carton and blister
The applicant has provided the proposed wording for the packaging and mock-ups of the 60 pack size of tablets. Confirmation has been provided that mock-ups of packaging for
other proposed pack sizes will be provided before marketing of those packs takes place in the UK.

7. CONCLUSIONS
The data submitted with the applications are acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

As these are duplicate applications, no new clinical data have been supplied and none are required.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to previously granted applications for Mabron 100mg, 150mg and 200mg Prolonged-Release Tablets (PL20117/0003-0005).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference product. Extensive clinical experience with tramadol hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk:benefit is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 20/11/2006.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered</td>
</tr>
<tr>
<td></td>
<td>the applications valid on 30/01/2007.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information on</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 22/02/2008</td>
</tr>
</tbody>
</table>
MAROL 100MG PROLONGED-RELEASE TABLETS (PL 20117/0045)
MAROL 150MG PROLONGED-RELEASE TABLETS (PL 20117/0046)
MAROL 200MG PROLONGED-RELEASE TABLETS (PL 20117/0047)

**STEPS TAKEN AFTER ASSESSMENT**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Marol 100mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Marol Tablets are prolonged release tablet containing 100 mg of Tramadol hydrochloride.
For excipients, see section 6.1

3 PHARMACEUTICAL FORM
Prolonged release tablet.
Marol 100 mg tablets are off white, round biconvex tablets, 9.1 mm diameter

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:
\textit{Rare} (\( \geq 0.01\% - <0.1\% \)): blurred vision

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

Gastrointestinal disorders:
\textit{Very common} (\( \geq 10\% \)): nausea
\textit{Common} (\( \geq 1\% - 10\% \)): vomiting, constipation, dry mouth.
\textit{Uncommon} (\( \geq 0.1\% - <1\% \)): Retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating).

Skin and subcutaneous tissue disorders:
\textit{Common} (\( \geq 1\% - 10\% \)): sweating
\textit{Uncommon} (\( \geq 0.1\% - <1\% \)): dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal disorders:
\textit{Rare} (\( \geq 0.01\% - < 0.1\% \)): motorial weakness

Hepato-biliary disorders:
In a few isolated cases (\( \leq 0.01\% \)) an increase in liver enzyme values has been reported after use of tramadol.

Renal and urinary system disorders:
\textit{Rare} (\( \geq 0.01\% - < 0.1\% \)): micturition disorders (difficulty in passing urine and urinary retention).

Immune system disorders:
\textit{Rare} (\( \geq 0.01\% - < 0.1\% \)): 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 (Vd β = 203 ± 40 l). Protein binding is about 20%.

After administration of tramadol 100mg prolonged release tablets the maximum peak plasma concentration Cmax 141 ± 40 ng/ml is reached after 4.9 hours. After administration of tramadol 200mg prolonged release tablets a Cmax 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 t½β 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 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 individual 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
Morningside Healthcare Limited
115 Narborough Road
Leicester
LE3 0PA
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0045

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/02/2008
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 gastrointestinal 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 naloxone. 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 (Vd,β = 203 ± 40 l). Protein binding is about 20%.

After administration of tramadol 100mg prolonged release tablets the maximum peak plasma concentration Cmax 141 ± 40 ng/ml is reached after 4.9 hours. After administration of tramadol 200mg prolonged release tablets a Cmax 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

Morningside Healthcare Limited
115 Narborough Road
Leicester
LE3 0PA
UK

### 8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0046

### 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/02/2008

### 10 DATE OF REVISION OF THE TEXT

22/02/2008

### 11 DOSIMETRY (IF APPLICABLE)

### 12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
NAME OF THE MEDICINAL PRODUCT
Marol 200mg Prolonged-release tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Marol Tablets are prolonged release tablet containing 200 mg of Tramadol hydrochloride.

For excipients, see section 6.1

PHARMACEUTICAL FORM
Prolonged release tablet.

Marol 200 mg tablets are off white, capsule-shaped tablets, 17.1 mm long

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. Psychiatric 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 gastrointestinal 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 $\mu$, $\delta$, and $\kappa$-opioid receptors with a higher affinity for $\mu$-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 ($V_d \beta = 203 \pm 40 \text{l}$). 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 $t_{1/2}$ 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 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 $t_{1/2}$ (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
Morningside Healthcare Limited
115 Narborough Road
Leicester
LE3 0PA
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0047

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/02/2008

10 DATE OF REVISION OF THE TEXT
22/02/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
<th>Brand</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>100mg</td>
<td>Prolonged Release Tablets</td>
<td>MAROL 100MG</td>
<td>MORPHINE HEALTHCARE LTD</td>
</tr>
<tr>
<td></td>
<td>(Tramadol Hydrochloride)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150mg</td>
<td>Prolonged Release Tablets</td>
<td>MAROL 150MG</td>
<td>MORPHINE HEALTHCARE LTD</td>
</tr>
<tr>
<td></td>
<td>(Tramadol Hydrochloride)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200mg</td>
<td>Prolonged Release Tablets</td>
<td>MAROL 200MG</td>
<td>MORPHINE HEALTHCARE LTD</td>
</tr>
<tr>
<td></td>
<td>(Tramadol Hydrochloride)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MHRA PAR – Marol 100, 150 and 200mg Prolonged-Release Tablets (PL 20117/0045-7)
Marol 100 mg, 150 mg and 200 mg Prolonged Release Tablets
(Tramadol hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it onto others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Marol Tablets is and what it is used for
2. Before you take Marol Tablets
3. How to take Marol Tablets
4. Possible side effects
5. How to store Marol Tablets
6. Further information

1. WHAT MAROL Tablets IS AND WHAT IT IS USED FOR

The name of your medicine is Marol 100 mg, 150 mg or 200 mg Prolonged-release Tablets.

Each prolonged release tablet contains 100 mg, 150 mg or 200 mg of tramadol hydrochloride. Tramadol, the active substance, is a centrally acting opioid analgesic that is used for the treatment of moderate to severe pain.

Marol Prolonged-release tablets is referred to as Marol tablets below.

2. BEFORE YOU TAKE Marol Tablets

Do not take Marol Tablets:
- If you are allergic (hypersensitive) to tramadol hydrochloride or any of the other ingredients of Marol Tablets.
- If you are pregnant (see Pregnancy and breast feeding below).
- If you have recently drunk too much alcohol or taken too many sleeping tablets, other painkillers or any medicines that affect your mood such as antidepressant medicines.
- If you are, or have taken in the last two weeks, an antidepressant medicine called a monoamine oxidase inhibitor (MAOI), such as phenelzine or moclobemide.

Take special care with Marol Tablets:
- You have recently had any head injuries, suffered from any severe headaches or felt sleepy for no reason (especially after an accident).
- You have recently had an accident where you may still be in shock.
- You find it difficult to breathe, or your breathing is a lot slower than normal.
- You have, or have had, an addiction to opioid analgesics (such as morphine, diamorphine or codeine).
- You have epilepsy.

If any of the above apply to you, please talk to your doctor or pharmacist for advice if you have not already done so.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular, you should talk to your doctor before taking Marol if you are taking any of the following:
- A monoamine oxidase inhibitor (MAOI) (such as isocarboxazid, phenelzine or trycypromine).
- Alcohol.
- Medicines that cause drowsiness (such as sleeping tablets, antidepressants, some other painkillers).
- Other opioid painkillers (analgesics) (such as buprenorphine, nalbuphine or pentazocine).
- Carbamazepine (for epilepsy).
- Antidepressant or antipsychotic medicines (such as fluoxetine, citalopram, amitriptyline, imipramine, chlorpromazine, haloperidol or sulpiride).
- Medicines to thin the blood (such as warfarin).
- Ketoconazole (an medicine for treating fungal infections).
- Erythromycin (an antibiotic for treating infections).

Taking with food and drink
Marol tablets can be taken before, with or after food. You should NOT drink alcohol whilst taking these tablets.

Pregnancy and breast-feeding
Marol tablets should not be taken during pregnancy as it may affect the unborn child. If you become pregnant while taking Marol you should talk to your doctor immediately.

It is also not advised to take the tablets whilst breast-feeding. However, if your doctor feels it necessary, you do not have to stop breast-feeding for a once only dose of Marol tablets.

Driving and using machines
Marol tablets can affect your ability to drive and operate machinery, particularly when combined with other medicines that can cause drowsiness. Therefore, driving and operating machinery is not advised whilst taking these tablets.

3. HOW TO TAKE MAROL Tablets

Always take Marol tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The tablets should be swallowed whole, without breaking or chewing, with a glass of water. The usual dose is:

Adults: The usual starting dose is one 100 mg tablet twice a day (in the morning and evening). If this is not sufficient to kill the pain, your doctor may give you either one 150 mg tablet or one 200 mg tablet twice a day.

Your doctor will prescribe the lowest possible dose that provides pain relief. This is usually no more than 400 mg (two 200 mg tablets) a day except in special circumstances.

Marol tablets should not be used for any longer than is absolutely necessary. If you need to take these tablets for a long period your doctor will monitor you regularly.

Children (under 12 years old): Marol tablets are not suitable for children under 12 years old.

Elderly patients over 75 years old: Your doctor may need to prescribe a different dose to those listed above.

Patients with kidney or liver problems: Marol tablets are not recommended for patients with severe liver or kidney problems. If you have kidney or liver problems that are not severe, your doctor may prescribe a lower dose.

If you take more Marol Tablets than you should
Immediately contact your doctor or your nearest hospital casualty department immediately. Please take any remaining medicine with you in the carton in which it came so that staff will know what has been taken.

If you forget to take Marol Tablets
Take it as soon as you remember then continue as before. If it is nearly time for your next tablet, leave the missed dose and continue as before. Do not take any more tablets in one day than your doctor has prescribed.
Do not take a double dose to make up for a forgotten dose.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Marol Tablets can cause side effects, although not everybody gets them.

Stop taking the tablets and tell your doctor immediately if you experience any of the following rare effects:

- A severe or itchy skin rash, especially if this shows blistering and there is soreness of the eyes, mouth or genital organs.
- Swelling of the hands, face, lips or tongue.
- Difficulty breathing, or wheezing.

These are all possible signs of a severe allergic reaction.

Very common side effects (affecting more than 10 people in every 100) are nausea and dizziness.

Common side effects (affecting 1 to 10 people in every 100) include:
- headache;
- drowsiness;
- being sick (vomiting);
- constipation;
- dry mouth;
- sweating.

Uncommon side effects (affecting less than 1 person in every 100) include:
- being aware of your heartbeat (heart palpitations);
- heart beating faster than normal;
- dizziness or fainting when standing from a sitting or lying position (hypotension);
- a collapse of the heart and blood supply;
- itching;
- a feeling of pressure or bloating in the stomach;
- skin reactions, such as itching or a rash, reddening of the skin.

Rare side effects (affecting less than 1 person in every 1000) include:
- slower heartbeat than normal;
- an increase in your blood pressure;
- changes in appetite;
- tingling of the hands and feet;
- shaking (tremor);
- breathing slower than normal;
- convulsions (fits);
- seeing or hearing things that are not there (hallucinations);
- confusion;
- sleep disturbances and nightmares;
- changes in your mood, such as feeling unusually cheerful, or sometimes emotional and moody;
- changes in activity levels, this is usually feeling slower but some people may feel more energetic;
- a change in how you see things (perception) or your ability to make decisions;
- blurred vision;
- muscle weakness;
- difficulty in passing water;
- allergic reactions (see first warning above), you should immediately stop taking the tablets and talk to your doctor.

There have been a few isolated reports of an increase in liver enzymes. This would only usually be seen after you have had a blood test. Your doctor may check you for this, if the doctor thinks it’s necessary.

You may suffer from the following withdrawal effects when you stop taking these tablets:
- agitation
- anxiety
- nervousness
- problems sleeping
- feeling overactive
- shaking
- feeling sick or bloated, stomach pain or discomfort, and similar stomach problems

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE MAROL Tablets
Keep out of the reach and sight of children.

Do not use Marol tablets after the expiry date which is stated on the label carton and also on the blister

Do not store this medicine above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Marol contains
- The active substance is Tramadol hydrochloride
- The other ingredients are calcium hydrogen phosphate dihydrate (E341), hydroxypropylcellulose (E463), colloidal anhydrous silica (E551), and magnesium stearate (E470b).

What Marol Tablets looks like and contents of the pack
Marol 100 mg tablets are round, biconvex, off white, prolonged release tablets.
Marol 150 mg and 200 mg tablets are capsule-shaped, off white, prolonged release tablets.

All the strengths are available in either clear or opaque coloured blister packs and pots of 10, 20, 50, 75, 90, 100, 120, and 180 tablets but not all pack sizes may be marketed.

Marketing Authorisation Holder is
Morlingside Healthcare Limited, 115 Narborough Road, Leicester, LE30PA, UK

The Manufacturers are
PALDuven, Dijkgraaf, 6921, Medochemie Ltd, Facility A-Z, Rik Duiven, Ayios Athanasios, 1010, The Netherlands or Industrial Street, Limassol, Cyprus.

This leaflet was last approved in (MM/YYYY).

MHRA PAR – Marol 100, 150 and 200mg Prolonged-Release Tablets (PL 20117/0045-7)