

TRAMADOL CAPSULES 50MG

PL 20117/0086

UKPAR

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 12
Steps taken after authorisation – summary	
Summary of Product Characteristics	Page 13
Product Information Leaflet	Page 19
Labelling	Page 21

TRAMADOL CAPSULES 50MG PL 20117/0086

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited a Marketing Authorisation for the medicinal product Tramadol Hydrochloride 50mg Capsules (PL 20117/0086) on 16 March 2012. Tramadol Hydrochloride 50mg Capsules is a prescription only Medicine (POM).

Tramadol Hydrochloride 50mg Capsules is indicated for the treatment of moderate to severe pain. The active ingredient, tramadol hydrochloride belongs to a group of medicines known as opioids which act on the central nervous system. These relieve pain by acting on specific nerve cells of the spinal cord and brain.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Tramadol Hydrochloride 50mg Capsules outweigh the risks; hence Marketing Authorisation was granted.

TRAMADOL HYDROCHLORIDE 50MG CAPSULES PL 20117/0086

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Non-clinical assessment	Page 8
Clinical assessment	Page 9
Overall conclusions and risk assessment	Page 11

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Morningside Healthcare Limited a Marketing Authorisation for the medicinal product Tramadol Hydrochloride 50mg Capsules (PL 20117/0086) on 16 March 2012.

Tramadol Hydrochloride 50mg Capsules is a prescription only Medicine (POM) and is indicated for the treatment of moderate to severe pain.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Tramal 50mg Capsules (Grunethal GmbH, Germany), which was first authorised in Germany in 1980. The corresponding reference product in the UK is Zydol 50mg Capsules (PL 00020/0197; G D Searle & Co. Limited, UK), which was first authorised in the UK on 21 April 1994. This licence then underwent a change of ownership to Monsanto PLC (PL 08821/0005) on 20 December 1995.

The active ingredient, tramadol hydrochloride is an analgesic which belongs to the opioid family of compounds and is used to treat moderate to severe pain. It is an opioid receptor agonist and noradrenaline reuptake inhibitor.

Tramadol hydrochloride produces analgesia by two mechanisms; an opioid effect and an enhancement of serotonergic and adrenergic pathways.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A single-dose bioequivalence study, was submitted to support this application, comparing the pharmacokinetic profile of the test product, Tramadol Hydrochloride 50mg Capsules (Morningside Healthcare Limited), versus the reference product, Tramal 50mg Capsules (Grunethal GmbH, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Tramadol Hydrochloride 50mg Capsules outweigh the risks; hence the Marketing Authorisation was granted.

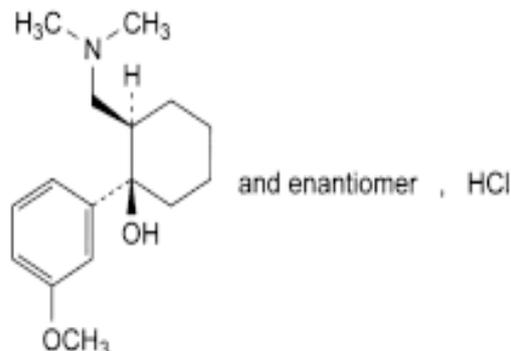
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Tramadol hydrochloride

Chemical Name: (1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride

Structure:



Molecular Formula: $C_{16}H_{26}ClNO_2$

Molecular weight: 299.8

Appearance: A white, bitter, odourless, crystalline powder. It is readily soluble in water and ethanol.

Tramadol hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance tramadol hydrochloride are covered by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest periods for the active substance when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely croscarmellose sodium, povidone (polyvinylpyrrolidone), microcrystalline cellulose, silicon dioxide, magnesium stearate, gelatin, titanium dioxide (E171), yellow iron oxide (E172), quinoline yellow (E104) and brilliant blue FD&C No.1 (E133). Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of yellow iron oxide (E172), quinoline yellow (E104) and brilliant blue FD&C No.1 (E133). Yellow iron oxide (E172) is controlled to its respective National Formulary specifications. Quinoline yellow (E104), yellow iron oxide (E172) and brilliant blue FD&C No.1 (E133) are also in compliance with current European Directives concerning use of colouring agents in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of gelatin and magnesium stearate, none of the excipients used contain materials of animal or human origin. All suppliers of gelatin and magnesium stearate have provided TSE Certificates of Suitability to show that appropriate measures are taken to reduce the risk of transmission of BSE/TSE, in line with current EU regulations.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable product that could be considered a generic medicinal product of Tramal 50mg Capsules (Grunethal GmbH, Germany).

Suitable pharmaceutical development data have been provided for this application.

Comparative dissolution and impurity profiles have been provided for this product and the respective reference product.

Manufacturing Process

Satisfactory batch formula has been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results. In addition confirmation has been provided that process validation studies will be performed on full scale production batches, in accordance with the process validation protocol.

Finished Product Specification

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The finished product is packaged in aluminium/polyvinylchloride blister packs. The blister strips are packed in cardboard cartons and are available in pack sizes of 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 capsules.

Not all pack sizes may be marketed. However, the Marketing Authorisation holder has committed to submitting mock-ups to the UK regulatory authorities for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

Stability

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 4 years with the storage conditions 'Store below 25°C, in the original package, to protect from moisture and light' has been accepted.

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling

The SmPC, PIL and labelling are satisfactory.

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, as amended. 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.

MAA Forms

The MAA form is satisfactory.

Expert Report

The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

The grant of Marketing Authorisation is recommended.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

As the pharmacodynamic, pharmacokinetic and toxicological properties of tramadol hydrochloride are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION

The grant of Marketing Authorisation is recommended.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of tramadol hydrochloride is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has conducted an open-label, randomised, single-dose, crossover, two period bioequivalence study comparing the test product Tramadol Hydrochloride 50mg Capsules versus the reference product Tramal 50mg Capsules (Grunethal GmbH, Germany) in healthy adult male subjects under fasted conditions. The objective of the pharmacokinetic study was to assess bioequivalence between the reference formulation and the test formulation, under fasting conditions after single oral administration.

All volunteers received a single oral dose of either the test or the reference product with 200ml of water, under fasted conditions. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 48 hours post dose. The washout period between the two treatment arms was one week.

Results for main pharmacokinetic parameters:

Test versus. Reference formulation

Parameters	Geometric Least Squares Mean			90% CI
	Reference product (Tramal 50mg Capsules)	Test product (Tramadol Hydrochloride 50mg Capsules)	Ratio (test/reference) %	
C_{max} (ng/ml)	156.836 (30.332)	168.032 (43.318)	105.69	97.92-114.07%
AUC_{0-t} (ng.h/ml)	1057.539 (441.896)	1079.848 (481.288)	101.39	96.15-106.92%
AUC_{0-∞} (ng.h/ml)	1199.0689 (508.362)	1220.769 (534.696)	101.40	96.73-106.31%
C_{max}	maximum plasma concentration			
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC_{0-∞}	area under the plasma concentration-time curve from time zero to infinity			
90% CI	geometric confidence interval (CI) calculated from ln-transformed data			

The 90% confidence intervals for AUC and C_{max} for test versus reference product for tramadol hydrochloride are within the acceptance criteria specified in the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)*. Thus, the data support the claim that the test product Tramadol Hydrochloride 50mg Capsules (Morningside Healthcare Limited) is bioequivalent to the reference product Tramal 50mg Capsules (Grunethal GmbH, Germany).

EFFICACY

The efficacy of tramadol hydrochloride is well-known. No new efficacy data have been submitted and none are required for application of this type.

SAFETY

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for application of this type. No new or unexpected safety issues were raised by the bioequivalence study.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

The SmPC, PIL and labelling are clinically acceptable. The SmPC is consistent with these for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

CONCLUSION

The grant of Marketing Authorisation is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Tramadol Hydrochloride 50mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of tramadol hydrochloride are well-known, no additional data were required.

EFFICACY

With the exception of the bioequivalence study, no new efficacy data were submitted and none are required for application of this type.

Bioequivalence has been demonstrated between the applicant's 50mg capsule strength and the reference product.

SAFETY

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for application of this type. No new or unexpected safety concerns arose from the bioequivalence study

PRODUCT LITERATURE

The SmPC, PIL and labelling are acceptable. The SmPC is consistent with these for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that this product can be considered equivalent to the reference product, Tramal 50mg Capsules (Grunenthal GmbH, Germany). Extensive clinical experience with tramadol hydrochloride is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.

TRAMADOL HYDROCHLORIDE 50MG CAPSULES PL 20117/0086

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Marketing Authorisation application on 15 April 2010.
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 22 April 2010.
- 3 Following assessment of the application the MHRA requested further information relating on the quality dossier on 20 September 2010, 29 June 2011 and 26 July 2011, and the clinical dossier on 07 September 2010.
- 4 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 02 June 2011, 20 July 2011 and 11 August 2011, and the clinical dossier on 16 February 2011.
- 5 The application was determined and granted on 16 March 2012.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tramadol Hydrochloride 50mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50mg tramadol hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Yellow/green hard gelatin capsule

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an analgesic. Tramadol Hydrochloride 50mg Capsules are indicated for the treatment of moderate to severe pain.

4.2 Posology and method of administration

Capsules should be swallowed whole with sufficient liquid. Capsules' intake is independent of meals.

In common with all analgesics, the dose should be adjusted according to the pain intensity and the response of the patient.

Adults and children, 12 years and over:

Dependent upon pain severity, the initial dose is 50mg or 100mg; with subsequent doses of either 50mg or 100mg, depending upon clinical need, every four to six hours.

In acute pain, an initial dose of 100mg is usually required. Chronic pain usually requires an initial dose of 50mg and then titrations according to pain severity.

Treatment should be limited and intermittent and given only when clinically required.

The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported.

The total daily oral dose should not exceed 400mg, except in special clinical circumstances.

Elderly:

No dosage adjustment is usually necessary although there is a slight increase in half life with increase in age. In volunteers aged over 75 years the elimination half-life of tramadol was increased by 17% following oral administration.

Renal impairment:

Elimination of tramadol may be prolonged in patients with renal impairment. No dosage adjustment is necessary, but dose interval should be prolonged to 12h for patients with creatinine clearance <30ml/min. In the case of severe renal impairment (creatinine clearance <10ml/min), the use of tramadol is not recommended.

Hepatic impairment:

Elimination of tramadol may be prolonged but no dosage adjustment is necessary. In severe hepatic impairment dose interval should be prolonged to 12h .

Renal dialysis:

Dosage adjustment following dialysis is not usually required due to the minimal elimination of tramadol by haemodialysis or haemofiltration.

Children less than 12 years of age:

Not recommended.

4.3 Contraindications

Contraindicated in patients who are:

- hypersensitive to tramadol or to any of the excipients
- acutely intoxicated with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs
- receiving, or have received in the preceding fourteen days, monoamine oxidase inhibitors.

- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Tramadol Hydrochloride 50mg Capsules may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure.

In patients sensitive to opiates the product should only be used with caution.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg).

In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see section 4.5). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment with Tramadol Hydrochloride 50 mg Capsules should only be carried out for short periods under strict medical supervision.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol Hydrochloride 50mg Capsules not be combined with MAO inhibitors (see section 4.3).

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Tramadol Hydrochloride 50mg Capsules.

Concomitant administration of Tramadol Hydrochloride 50mg Capsules with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section 4.8).

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, tricyclic anti-depressants, anti-psychotics and other seizure threshold lowering medicinal products to cause convulsions.

In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotonergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs) or with MAO inhibitors. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

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

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied (see section 4.8).

In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT₃ antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

When administered with coumarin anticoagulants interaction results in an increased INR according to isolated reports. Care should be taken when commencing treatment with tramadol in patients on anticoagulants.

4.6 Fertility, Pregnancy and lactation

Pregnancy:

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore Tramadol Hydrochloride 50mg Capsules should not be used in pregnant women.

Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Lactation:

During lactation about 0.1 % of the maternal dose is secreted into the milk. Tramadol Hydrochloride 50mg Capsules are not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

4.7 Effects on ability to drive and use machines

Tramadol Hydrochloride 50mg Capsules may cause drowsiness, this effect can be potentiated by alcohol and other CNS depressants; patients must be warned not to drive or operate machinery if affected.

4.8 Undesirable effects

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

Cardiovascular disorders:

uncommon ($\geq 1/1000$, $< 1/100$): cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

rare ($\geq 1/10000$, $< 1/1000$): bradycardia, increase in blood pressure

Nervous system disorders:

very common ($\geq 1/10$): dizziness

common ($\geq 1/100$, $< 1/10$): headache, somnolence

rare ($\geq 1/10000$, $< 1/1000$): changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.

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

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see sections 4.4 and 4.5).

Psychiatric disorders:

rare ($\geq 1/10000$, $< 1/1000$): hallucinations, confusion, sleep disturbance, anxiety and nightmares. Psychic adverse reactions may occur following administration of Tramadol Hydrochloride 50mg Capsules which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). Dependence may occur.

Eye disorders:

rare ($\geq 1/10000$, $< 1/1000$): blurred vision

Respiratory disorders:

rare ($\geq 1/10000$, $< 1/1000$): dyspnoea

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

Gastrointestinal disorders:

very common ($\geq 1/10$): nausea

common ($\geq 1/100$, $< 1/10$): vomiting, constipation, dry mouth

uncommon ($\geq 1/1000$, $< 1/100$): retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea

Skin and subcutaneous disorders:

common ($\geq 1/100$, $< 1/10$): sweating

uncommon ($\geq 1/1000$, $< 1/100$): dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal disorders:

rare ($\geq 1/10000$, $< 1/1000$): motorial weakness

Hepatobiliary disorders:

In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Renal and urinary disorders:

rare ($\geq 1/10000$, $< 1/1000$): micturition disorders (difficulty in passing urine, dysuria and urinary retention)

General disorders:

common ($\geq 1/100$, $< 1/10$): fatigue

rare ($\geq 1/10000$, $< 1/1000$): allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms.

4.9 Overdose

Symptoms: Typical of opioid analgesics, including vomiting, cardiovascular collapse, miosis, seizures, respiratory depression, sedation and coma.

Treatment: Institution of supportive measures to maintain patency of the airway and the cardiovascular function. Respiratory depression may be reversed by the administration of Naloxone; administration of Diazepam can be used to control fits.

Haemodialysis/haemofiltration leads to minimal serum elimination of tramadol, thus it is not suitable as a sole treatment for detoxification.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotheapeutic group: Analgesics ATC code: N02AX02

Tramadol Hydrochloride 50mg Capsules is a centrally acting analgesic, with non-selective agonist properties for the mu, delta and kappa opioid receptors, it shows a higher affinity for the mu receptor. Supplementary actions, apparently playing a part in analgesic efficacy, are the inhibition of neuronal reuptake of noradrenaline and the enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

5.2 Pharmacokinetic properties

After oral administration, tramadol is almost completely absorbed. Mean absolute bioavailability is approximately 70% following a single dose and increases to approximately 90% at steady state. Plasma protein binding of tramadol is approximately 20%. Approximately 90% is excreted via the kidneys with the remaining 10% excreted in the faeces.

The pharmacokinetic profile of tramadol is linear within the therapeutic dosage range.

The elimination half life of tramadol, in healthy young volunteers, is reported as 5.1h to 5.9h; it shows little age dependency although with increasing age there is a trend to increasing half life. In patients with impaired hepatic function (cirrhosis of the liver), the terminal half life increases by a factor of two to three times; similarly in patients with impaired renal function (creatinine clearance between 5 to 80ml/min), the terminal half life increases by a factor of one and a half to two times the normal.

Tramadol is metabolized by the cytochrome P450 isoenzyme CYP2D6. It undergoes biotransformation to a number of metabolites mainly by means of N and O demethylation. O desmethyl tramadol appear to be the most pharmacologically active metabolite showing analgesic activity in rodents. As humans excrete a higher percentage of unchanged tramadol than animals it is believed that the contribution made by this metabolite to analgesic activity is likely to be less in humans than animals. In human the plasma concentration of this metabolite is about 25% that of unchanged tramadol.

Since tramadol is eliminated both metabolically and renally, the terminal half-life $t_{1/2\beta}$ tramadol was a mean of 13.3 + 4.9.

5.3 Preclinical safety data

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dogs haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tramadol Hydrochloride 50mg Capsules capsules also contain;

Croscarmellose sodium

Povidone (polyvinylpyrrolidone)

Microcrystalline cellulose

Silicon dioxide

Magnesium stearate

Gelatin

Titanium dioxide

Iron oxide yellow

Quinoline yellow

Brilliant blue FD&C No. 1.

6.2 Incompatibilities

None known.

6.3 Shelf life

4 Years

6.4 Special precautions for storage

Tramadol Hydrochloride 50mg Capsules capsules should be stored below 25°C , in the original package, to protect from moisture and light.

6.5 Nature and contents of container

Tramadol Hydrochloride 50mg Capsules are presented in combination aluminium/polyvinylchloride blister packs of 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0086

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/03/2012

10 DATE OF REVISION OF THE TEXT

16/03/2012

MODULE 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tramadol Hydrochloride 50mg Capsules

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 on to 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 Tramadol Capsules are and what they are used for
2. Before you take Tramadol Capsules
3. How to take Tramadol Capsules
4. Possible side effects
5. How to store Tramadol Capsules
6. Further information

1. WHAT TRAMADOL CAPSULES ARE AND WHAT THEY ARE USED FOR

Tramadol hydrochloride is the active substance in Tramadol Capsules, it is a painkiller belonging to the class of opioids that acts on the central nervous system. It relieves pain by acting on specific nerve cells of the spinal cord and brain. Tramadol Capsules are used for the treatment of moderate to severe pain.

2. BEFORE YOU TAKE TRAMADOL CAPSULES

Do not take Tramadol Capsules

- if you are allergic (hypersensitive) to tramadol or any of the other ingredients of Tramadol Capsules;
- in acute poisoning with alcohol, sleeping pills, pain relievers or other psychotropic medicines (medicines that affect mood and emotions);
- if you are also taking monoamine oxidase (MAO) inhibitors (certain medicines used for treatment of depression) or have taken them in the last 14 days before treatment with Tramadol Capsules (see "Taking other medicines");
- if you are dependent upon strong pain relievers (those acting on the central nervous system - opioids)
- if you are an epileptic and your fits are not adequately controlled by treatment;
- as a substitute in drug withdrawal.

Take special care with Tramadol Capsules

- if you think that you are addicted to other pain relievers (opioids);
 - if you suffer from consciousness disorders (if you feel that you are going to faint);
 - if you are in a state of shock (cold sweat may be a sign of this);
 - if you suffer from increased pressure in the brain (possibly after a head injury or brain disease);
 - if you have difficulty in breathing;
 - if you have epilepsy or fits because the risk of a fit may increase;
 - if you suffer from a liver or kidney disease;
- In such cases please consult your doctor before taking the medicine.

Epileptic fits have been reported in patients taking tramadol at the recommended dose level. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg).

Please note that Tramadol Capsules may lead to physical and psychological addiction. When Tramadol Capsules are taken for a long time, its effect may decrease, so that higher doses have to be taken (tolerance development).

In patients with a tendency to abuse medicines or who are dependent on medicines, treatment with Tramadol Capsules should only be carried out for short periods and under strict medical supervision.

Please also inform your doctor if one of these problems occurs during Tramadol Capsules treatment or if they applied to you in the past.

Taking other medicines

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

It is important to tell the doctor if you are taking:

- A group called monoamine oxidase inhibitors (MAOIs), or if you have taken them in the previous fourteen days.
- Carbamazepine (for epileptic fits).
- Buprenorphine, nalbuphine, or pentazocine (pain killers).
- Ondansetron (used to stop you feeling sick).
- Anti-depressants (5HT and noradrenaline potentiating) including serotonin reuptake inhibitors (SSRIs).
- Sedative medicines such as tranquillisers, sleeping pills, antidepressants and strong pain relievers (morphine, codeine, pethidine). You may feel excessively drowsy or feel that you might faint.
- Tricyclic antidepressant and antipsychotic medicines. There may be an increased risk of epileptic fits.
- Blood thinning medicines, such as warfarin. The dose of these medicines may need reducing; otherwise there could be an increased risk of serious bleeding.
- Anticonvulsant drugs taken with tramadol can lower the seizure threshold and the risk of convulsions may increase in these patients.

Taking Tramadol Capsules with food and drink

Do not drink alcohol during treatment with Tramadol Capsules as it may increase the intensity of the side effects. Tramadol Capsules can be taken with or without food.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine. There is very little information regarding the safety of tramadol in human pregnancy. Therefore you should not use Tramadol Capsules if you are pregnant. Chronic use during pregnancy may lead to withdrawal symptoms in newborns.

Generally, the use of tramadol is not recommended during breast-feeding. Small amounts of tramadol are excreted into breast milk. On a single dose it is usually not necessary to interrupt breast-feeding. Please ask your doctor for advice.

Driving and using machines

Tramadol Capsules can cause drowsiness and dizziness, and blurred vision. Because of this Tramadol Capsules can affect your ability to drive and operate machinery. Do not drive a car or do other activities that need you to be alert, until you know how tramadol affects you.

3. HOW TO TAKE TRAMADOL CAPSULES

Always take Tramadol Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The dosage should be adjusted to the intensity of your pain and your individual pain sensitivity. In general the lowest pain-relieving dose should be taken.

Unless otherwise prescribed by your doctor, the usual dose is:

Adults and adolescents from the age of 12 years

1 (One) or 2 (two) Tramadol Capsules (equivalent to 50 mg 100 mg) with subsequent doses of 50 mg or 100 mg, every 4 (four) to 6 (six) hours.

Do not take more than 8 (eight) Tramadol Capsules (equivalent to 400 mg tramadol hydrochloride) daily, except if your doctor has instructed you to do so.

Dependent upon pain severity, your doctor may prescribe a different, more appropriate dosage of Tramadol Capsules if necessary.

Children

Tramadol Capsules are not suitable for children below the age of 12 years.

Elderly patients

In elderly patients (above 75 years) the excretion of tramadol may be delayed. If this applies to you, your doctor may alter your dose.

Severe liver or kidney disease (insufficiency)/dialysis patients

Patients with severe liver and/or kidney insufficiency should not take Tramadol Capsules.

If in your case the insufficiency is mild or moderate, your doctor may alter your dose.

How and when should you take Tramadol Capsules

Always swallow Tramadol Capsules whole, not divided or chewed, with sufficient liquid,

preferably in the morning and evening. You may take the capsule on an empty stomach or with meals.

How long should you take Tramadol Capsules
You should not take Tramadol Capsules for longer than necessary. If you need to be treated for a longer period, your doctor will check at regular short intervals (if necessary with breaks in treatment) whether you should continue to take Tramadol Capsules and at what dose. If you have the impression that the effect of Tramadol Capsules is too strong or too weak, talk to your doctor or pharmacist.

If you take more Tramadol Capsules than you should

If you have taken too many Tramadol Capsules you should immediately contact your doctor, nearest hospital or clinic. The possible symptoms that may occur are: pin-point pupils, vomiting, a fall in blood pressure, a fast heartbeat, collapse, disturbed consciousness including coma (deep unconsciousness), epileptic fits and difficulties in breathing.

If you forget to take Tramadol Capsules

If you forget to take a dose, leave out the missed dose and take the next dose on time. Never take two doses together.

If you stop taking Tramadol Capsules

If you interrupt or finish treatment with Tramadol Capsules too soon, pain is likely to return. If you wish to stop treatment on account of unpleasant effects, please tell your doctor. Generally there will be no after effects when treatment with Tramadol Capsules is stopped. However, on rare occasions, people who have been taking Tramadol Capsules for some time may feel unwell if they abruptly stop taking them. They may feel agitated, anxious, nervous or shaky. They may be hyperactive, have difficulty sleeping and have stomach or bowel disorders. Very few people may get panic attacks, hallucinations, unusual perceptions such as itching, tingling and numbness, and noise in the ears (tinnitus). If you experience any of these complaints after stopping Tramadol Capsules, please consult your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tramadol Capsules can cause side effects, although not everybody gets them.

In case one of the following situations occur, see your doctor straight away:

- allergic reactions e.g. difficulty in breathing, wheezing, swelling of skin (occurs rarely),
- swollen face, tongue and/or throat and/or difficulty to swallow or hives together with difficulties in breathing (occurs rarely),
- shock/sudden circulation failure (occurs rarely).

Usually the frequency of side effects is classified as follows:

- very common (more than 1 out of 10 persons),
- common (more than 1 out of 100 persons),
- uncommon (more than 1 out of 1,000 persons),
- rare (more than 1 out of 10,000 persons)
- very rare (less than 1 out of 10,000 persons).

The most common side effects during treatment with Tramadol Capsules are nausea and dizziness, which occur in more than in 1 out of 10 patients.

Heart and blood circulation disorders

uncommon: effects on the heart and blood circulation (pounding of the heart, fast heart beat, feeling faint or collapse). These adverse effects may particularly occur in patients in an upright position or under physical strain.

rare: slow heart beat, increase in blood pressure.

Nervous system disorders

very common: dizziness.

common: headaches, drowsiness.

rare: changes in appetite, abnormal sensations (e.g. itching, tingling, numbness), trembling, slow breathing, epileptic fits, muscle twitches, uncoordinated movement, transient loss of consciousness (syncope).

If the recommended doses are exceeded, or if other medicines that depress brain function are taken at the same time, breathing may slow down. Epileptic fits have occurred mainly at high doses of tramadol or when tramadol was taken at the same time as other medicines which may induce fits.

Psychiatric disorders

rare: hallucinations, confusion, sleep disorders, anxiety and nightmares. Psychological complaints may appear after treatment with Tramadol Capsules. Their intensity and nature may vary (according to the patient's personality and length of therapy). These may appear as a change in mood (mostly high spirits, occasionally irritated mood), changes in activity (slowing down but sometimes an increase in activity) and being less aware and less able to make decisions, which may lead to errors in judgement. Dependence may occur.

Eye disorders

rare: blurred vision.

Respiratory disorders

rare: shortness of breath (dyspnoea).

Worsening of asthma has been reported, however it has not been established whether it was caused by tramadol.

Stomach and bowel disorders

very common: feeling sick.

common: being sick, constipation, dry mouth.

uncommon: urge to be sick (retching), stomach trouble (e.g. feeling of pressure in the stomach, bloating), diarrhoea.

Skin disorders

common: sweating

uncommon: skin reactions (e.g. itching, rash).

Muscle disorders

rare: weak muscles.

Liver and biliary disorders

very rare: increase in liver enzyme values.

Urinary disorders

rare: passing water difficult or painful, less urine than normal.

General disorders

common: tiredness, weariness, weakness, low energy.

If Tramadol Capsules is taken over a long period of time dependence may occur, although the risk is very low. When treatment is stopped abruptly signs of withdrawal may appear (see "If you stop taking Tramadol Capsules").

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 TRAMADOL CAPSULES

Keep out of the reach and sight of children.

Tramadol Capsules should be stored below 25°C, in the original package, to protect from moisture and light.

Do not use Tramadol Capsules after the expiry date which is stated on the blister and the carton after "exp". The expiry date refers to the last day of that month.

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 Tramadol Capsules contain

Each capsule contains 50 mg tramadol hydrochloride.

The other ingredients are croscarmellose sodium, povidone (polyvinylpyrrolidone), microcrystalline cellulose, silicon dioxide, magnesium stearate, gelatin, titanium dioxide, iron oxide yellow, quinoline yellow and Brilliant blue FD&C No. 1.

What Tramadol Capsules look like and contents of the pack

Tramadol Capsules are yellow and green.

Tramadol Capsules are presented in combination aluminium/polyvinylchloride blisters strips and are supplied in boxes of 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Morningside Healthcare Limited
115 Narborough Road
Leicester, LE3 0PA, UK

Manufacturer:
Medochemie Ltd
Central Factory (Plant A)
1-10 Constantinoupoleos Str., Zakaki, Limassol, Cyprus
Facility A-Z, Mich. Erakleous Str., Ag. Athanasios, Industrial Area, Limassol, Cyprus

This leaflet was last revised in February 2012

MODULE 4

LABELLING

