

Public Assessment Report

Tramadol 50mg Capsules

PL 17907/0110

TRAMADOL 50MG CAPSULES

PL 17907/0110

UKPAR

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TRAMADOL 50MG CAPSULES

PL 17907/0110

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Bristol Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Tramadol 50mg Capsules (PL 17907/0110). This is a prescription only medicine [POM] used to treat or prevent moderate to severe pain.

This product contains tramadol, which acts on pathways known as opioid receptors in the brain and spinal cord to relieve pain.

The clinical data presented to the MHRA, before licensing, demonstrated that Tramadol 50mg Capsules is essentially similar or equivalent to the approved product, Zydol 50mg Capsules, and as such can be used interchangeably.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Tramadol 50mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

TRAMADOL 50MG CAPSULES

PL 17907/0110

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Tramadol 50mg Capsules (PL 17907/0110) to Bristol Laboratories Limited on 27 June 2006. Tramadol 50mg Capsules is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Tramal Capsules, which was first authorised in Germany in 1980. The UK version is Zydol 50mg Capsules.

This product contains tramadol hydrochloride and is indicated for the management (treatment and prevention) of moderate to severe pain.

Tramadol is a centrally acting analgesic. It is a non-selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenalines and enhancement of serotonin release.

PHARMACEUTICAL ASSESSMENT

LICENCE No.: PL 17907/0110
PROPRIETARY NAME: Tramadol 50mg Capsules
ACTIVE(S): Tramadol hydrochloride
COMPANY NAME: Bristol Laboratories Ltd
EC ARTICLE: 10.1(a)(iii)
LEGAL STATUS: Prescription Only Medicine (POM)

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

The batch release site is Bristol Laboratories Ltd, Hertfordshire. Evidence of GMP compliance has been provided.

INTRODUCTION

This standard national abridged application is for an oral hard gelatin capsule containing 50mg tramadol hydrochloride. The drug substance is indicated for the prevention and treatment of moderate to severe pain. The usual adult dose is 50-100mg 3-4 times daily.

The originator product is Tramal Capsules, from Grunenthal GmbH and was first authorised in Germany in 1980. A UK version of the product is available as Zydol 50mg Capsules, PL 08821/0005, granted on 17 November 1994 (as PL 00020/0197), and is currently marketed. The UK reference product has been used in the biostudy.

DRUG SUBSTANCE

A Certificate of Suitability for the drug substance, tramadol, is provided.

Control of drug substance

Specification

A suitable drug substance specification has been provided.

Stability

Samples of 7 batches of tramadol hydrochloride were placed on stability. All batches used in the stability met the Ph.Eur. specification throughout the trials. No adverse trends were observed for any parameters tested. The results of the stability studies indicate that tramadol is stable.

DRUG PRODUCT

Description and composition of the drug product

Tramadol 50 mg Capsules are hard gelatin capsules, size 3, having a green cap and yellow body filled with a homogenous white to off-white powder containing 50mg of the drug substance tramadol hydrochloride.

Composition of Tramadol 50 mg Capsules

Name	Function	Reference to Standards
Drug substance		
Tramadol hydrochloride	Drug substance	Ph.Eur
Inactive ingredients		
Microcrystalline cellulose	Diluent	Ph.Eur
Sodium starch glycolate	Disintegrant	Ph.Eur
Purified water*	Solvent	Ph.Eur
Colloidal anhydrous silica	Glidant	Ph.Eur
Magnesium stearate	Lubricant	Ph.Eur
Empty hard gelatin capsule shell		HSE
Cap		
Yellow ferric oxide (E172)		USNF
Indigo carmine (E132)		Ph.Eur
Titanium dioxide (E171)		Ph.Eur
Sodium lauryl sulphate		Ph.Eur
Methyl parahydroxybenzoate (E218)		Ph.Eur
Propyl parahydroxybenzoate (E216)		Ph.Eur
Water		Ph.Eur
Gelatin		Ph.Eur
Body		
Yellow ferric oxide (E172)		USNF
Titanium dioxide (E171)		Ph.Eur
Sodium lauryl sulphate		Ph.Eur
Methyl parahydroxybenzoate (E218)		Ph.Eur
Propyl parahydroxybenzoate (E216)		Ph.Eur
Water		Ph.Eur
Gelatin		Ph.Eur

* Not present in the final product.

Tramadol 50 mg Capsules are packaged in opaque PVdC/PVC/aluminium blisters of 10 capsules (packs of 10, 20 or 100 capsules).

Pharmaceutical Development

Drug substance

The body of data provided for the drug substance is satisfactory.

Excipients

The formulation incorporates conventional excipients which are controlled by Ph.Eur. monographs. It is stated that all excipients present in the capsule fill of the proposed commercial formulation are those known to be in the reference product. These are

microcrystalline cellulose (diluent), sodium starch glycollate (disintegrant), silica colloidal anhydrous (glidant), magnesium stearate (lubricant), and purified water (granulation solvent).

Drug Product

Formulation development

The objective of the development programme was to formulate a stable formulation of Tramadol 50 mg Capsules comparable in performance to Zydol Capsules.

The data provided demonstrated that a satisfactory formulation and method had been developed. Comparative *in vitro* dissolution and impurity testing satisfied the claim of essential similarity. Confirmation has been provided by the bioequivalence study.

Container closure system

The stability studies at real time and accelerated conditions have shown that the drug product is stable in PVdC/PVC/Aluminium blisters. The proposed packaging is therefore considered to be suitable for Tramadol 50 mg Capsules.

Microbiological attributes

Tramadol 50 mg Capsules have been shown to comply with the European Pharmacopoeia's microbiological limits.

Manufacture

Manufacture(s)

Batch release takes place at Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts HP4 1EG.

Batch formula

The batch formulae for production scale batches of Tramadol 50 mg Capsules are provided.

Description of manufacturing process and process controls

Control of critical steps and intermediates

A flow diagram of the manufacturing procedure together with in-process controls has been provided.

Process validation and/or Evaluation

Process validation for 3 batches has been performed, demonstrating that the process produces a suitable drug product.

The first full scale commercial production batches manufactured will be validated according to a validation protocol provided. The protocol follows the 'Process Validation Scheme' in Annex 1 of the CPMP Guideline on Process Validation (CPMP/QWP/848/96). A report of

the process validation will be generated on completion of the studies. Any significant deviations will be reported to the regulatory authorities immediately.

Control of excipients

Specifications

Analytical procedures

Their respective Ph.Eur. monographs controls the excipients, including the purified water used as the granulating fluid. Analytical procedures for the excipients are performed as per the monographs specified. Certificates of Analysis are provided as evidence of compliance with the proposed specifications.

It has been confirmed that all colouring materials used in the manufacture of the capsules comply with Directive 2004/47/EC.

Excipients of animal or human origin

The gelatin present in the gelatin capsule is from an animal source. Certificates of Suitability for TSE have been provided by the suppliers of gelatin.

Suppliers of all the other excipients have certified that the materials are not from animal sources.

Control of drug product

Specification

An acceptable finished product specification has been provided.

Batch analysis

Batch analysis data are provided for 3 batches of Tramadol 50 mg Capsules. The batch analysis demonstrated compliance with the specification.

Characterisation of impurities

The limits for related substances are satisfactorily based on the batch and stability analytical results.

Justification of specification(s)

The applicant has included a justification for the proposed specification and limits.

Average weight, uniformity of weight, dissolution, disintegration, and microbial limits have been set according to the general compendial standards.

Assay and related substances have been set as per Directive 75/318 EEC.

Reference standards or materials

Batch data for the current working standard is presented. The Certificate of Analysis is provided.

Container closure system

The capsules are packed in opaque PVdC/PVC/aluminium blister packs. Each pack contains 10, 20 or 100 capsules. The blisters are constructed of PVdC, coated PVC and Aluminium foil.

The packaging is standard and compliance of the packaging to the requirements of Directive 94/62/EC, 90/128/EC, 2002/72/EC, 97/48/EC and 78/142/EC are stated.

Stability

Samples were packed in the marketing pack at 25°C/60%RH and 40°C/75%RH. Test methods were the same as those used for release testing.

The results indicate a stable product. A shelf-life of 3 years is proposed for Tramadol 50mg Capsules when stored below 25°C and in the original packaging. This is satisfactory.

ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

Satisfactory.

OTHER INFORMATION

Bioavailability/Bioequivalence

See Clinical Assessment report

Guideline compliance

The application has been prepared in line with current guidelines.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

LICENCE No.: PL 17907/0110
PROPRIETARY NAME: Tramadol 50mg Capsules
ACTIVE(S): Tramadol hydrochloride
COMPANY NAME: Bristol Laboratories Ltd
EC ARTICLE: 10.1(a)(iii)
LEGAL STATUS: Prescription Only Medicine (POM)

INTRODUCTION

This abridged application is for 50mg capsules of tramadol hydrochloride in the treatment of moderate to severe pain.

BACKGROUND

Bristol Laboratories Ltd have submitted a Marketing Authorisation Application for the above 50mg capsule of tramadol hydrochloride. Essential similarity is claimed to the product from Grunenthal marketed worldwide in the form of immediate release capsules containing 50mg of tramadol hydrochloride. In the UK these have been marketed as Zydol 50mg Capsules (PL 08821/0005, previously PL 00020/0197) since 1994.

Approval of the licence will enable the applicant to market the product under the generic label.

INDICATIONS

The treatment and prevention of moderate to severe pain.

DOSE & DOSE SCHEDULE

The usual dose in adults is 50-100mg (1-2 capsules) 3 to 4 times a day.

Appropriate starting and maintenance doses for use in adults and children are delineated in part 4.2 of the SPC.

TOXICOLOGY

No formal data are presented and none are required for this application. The toxicological and pharmacological profile of tramadol is well-known and understood.

CLINICAL PHARMACOLOGY

No formal pharmacokinetic or pharmacodynamic data are presented and none are required for this application.

The dissolution profiles of the test product have been compared with the reference product, "Zydol Capsules". The test product can be considered to be similar to the reference product *in vitro*, and the dissolution characteristics of the formulation should not have any adverse impact on the absorption of the drug from the gastrointestinal tract.

Single bioequivalence study

An open label, randomised, two-treatment, two-sequence, two-period, two-way, cross-over, single-dose bioavailability study of the test product, Tramadol 50mg Capsules, compared with Zydol 50mg Capsules (containing tramadol hydrochloride 50mg) in healthy, adult, male, human subjects under fasting conditions.

Before the study began, the protocol was reviewed and approved by an ethics committee. All subjects gave signed informed consent prior to participation and all had a comprehensive clinical examination and laboratory tests to assess their state of health. Only those subjects who complied with all inclusion and exclusion criteria were considered suitable for acceptance into the study.

Subjects were admitted to the clinical unit on the evening before the first dosing day for a final health check and to ensure compliance with the fasting requirements. Allocation to the test or reference product was according to a predetermined random table. The subjects were fasted before dosing and for 4 hours afterwards.

Blood samples were taken before dosing (baseline sample) and then at 30 minutes and at 15 minutes intervals thereafter until 3½ hours, when samples were taken at 4, 5, 6, 8, 12, 16 and 24 hours after dosing.

They returned after a suitable washout-period for the second study phase when they underwent the same procedures as before but were given the alternate medication to take for the dose profile. All 26 subjects completed the study but only subject numbers 1-24 were included in the final analysis as #25 and #26 were held as reserves in case of drop-outs.

Plasma samples were analysed for both the parent drug, tramadol, and its main active metabolite, O-desmethyl tramadol using a validated method.

From the individual plasma drug time-concentrations, pharmacokinetic parameters for C_{max} , T_{max} , and AUC_{0-t} and $AUC_{0-\infty}$ were calculated.

The 90% CIs for the ratio of the test/reference mean values for both the parent drug and the main metabolite were within the normal acceptance limits of 80-125%. It can therefore be concluded that the two products are bioequivalent.

Apart from two minor adverse events that rapidly resolved and two LFTs that were marginally raised, no other clinically significant abnormalities were detected.

EFFICACY

No new efficacy data are presented in this application and none are required.

SAFETY

No formal safety data are presented and none are required.

EXPERT REPORTS

There is a concise but adequate clinical expert report. It includes a critique of the single dose bioequivalence study. The *curriculum vitae* of the clinical expert is included, as are those for the preclinical and pharmaceutical experts.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Being very close to the SPC for Zydol, this is satisfactory.

LABELLING

The labelling is medically satisfactory.

DISCUSSION

This application for a 50mg capsule of tramadol hydrochloride has used the Zydol 50mg capsules marketed currently by Monsanto plc in the UK as cross-referenced product.

The clinical expert has satisfactorily addressed the various issues, including the single dose bioequivalence study.

RECOMMENDATION

A marketing authorisation may be granted.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Tramadol 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.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Tramadol 50mg Capsules and Zydol 50mg Capsules (PL 08821/0005), the UK version of Tramal Capsules.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those of Zydol 50mg Capsules.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with tramadol is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

TRAMADOL 50MG CAPSULES

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Tramadol 50mg Capsules on 3 August 2004.
2	The MHRA's assessment of the submitted clinical data was completed on 27 January 2005.
3	Further information (clinical) was requested from the company on 2 February 2005.
4	The applicant's response to further information (clinical) request was received on 13 April 2005.
5	The MHRA's assessment of the submitted quality data was completed on 7 June 2005.
6	The applicant's response to further information request (quality) was received on 13 July 2005.
7	Further information (quality) was requested from the company in a letter dated 18 January 2006.
8	The applicant's response to further information request (quality) was dated 6 March 2006.
9	The MHRA completed its assessment of the application on 26 June 2006.
10	The application was determined on 27 June 2006.
11	An application to include an additional blister pack size of 30 tablets was approved on 2 September 2006.

TRAMADOL 50MG CAPSULES

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tramadol 50 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Tramadol 50 mg Capsule contains 50 mg tramadol hydrochloride.

For excipients, see 6.1 ('List of Excipients').

3 PHARMACEUTICAL FORM

Green/Yellow coloured hard gelatin capsules for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Management (treatment and prevention) of moderate to severe pain.

4.2 Posology and method of administration

As with all analgesic drugs, the dose of Tramadol Capsules should be adjusted according to the severity of the pain and the clinical response of the individual patient.

Adults and children aged 12 years and over

Oral administration

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

Pain Associated with Chronic Conditions: Use an initial dose of 50 mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see section 4.4 Special Warnings and Precautions for Use).

A total daily oral dose of 400 mg should not be exceeded except in special clinical circumstances.

Capsules should be swallowed whole, not divided or chewed, with sufficient liquid, and independent of meals.

Elderly

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

Renal impairments/ renal dialysis

The elimination of tramadol may be prolonged. The usual initial dosage should be used. For patients with creatinine clearance <30ml /min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance <10ml/min). As tramadol is only removed very slowly by haemodialysis or haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

Hepatic impairment

The elimination of tramadol may be prolonged. The usual initial dosage should be used but in severe hepatic impairment the dosage interval should be increased to 12 hours.

Children under 12 years

Not recommended.

4.3 Contraindications

Tramadol 50 mg Capsules should not be administered to patients who have previously demonstrated hypersensitivity towards it or any of the excipients (see Section 6.1 'List of Excipients') or in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. In common with other opioid analgesics it should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5 'Interaction with Other Medicinal Products and Other Forms of Interaction').

4.4 Special warnings and precautions for use

Warnings

At therapeutic doses, Tramadol Capsules have the potential to cause withdrawal symptoms. Rarely cases of dependence and abuse have been reported.

At therapeutic doses withdrawal symptoms have been reported at a reporting frequency of 1 in 8,000. Reports of dependence and abuse have been less frequent.

Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

In patients with a tendency to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.

Tramadol Capsules are not suitable as a substitute in opioid-dependent patients. Although they are opioid antagonists, Tramadol Capsules cannot suppress morphine withdrawal symptoms.

Precautions

Tramadol Capsules should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.

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

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

In one study using a nitrous oxide/ opioid (Tramadol Capsules) anaesthetic technique (with only intermittent administration of enflurane ‘as required’) Tramadol Capsules were reported to enhance intra-operative recall. Hence their use during potentially very light planes of general anaesthesia should be avoided.

Two studies of Tramadol Capsule administration during anaesthesia comprising continuous administration of isoflurane have shown clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed, Tramadol Capsules may be used intra-operatively in the same way as other analgesic agents are routinely used.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol Capsules should not be combined with MAO inhibitors (see section 4.3 ‘Contraindication’).

Concomitant administration of Tramadol Capsules with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects (see section 4.8 ‘Undesirable Effects’).

Tramadol may increase the potential for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions (see section 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties). There is a theoretical possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.

Serotonergic drugs: Co-administration with serotonergic drugs, e.g. SSRIs or triptans, may lead to an increase of serotonin associated effects which can include serotonin syndrome.

There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR and so care should be taken when commencing treatment with tramadol in patients on anticoagulants.

Pharmacokinetic studies were conducted to investigate the effects of cimetidine, quinidine and carbamazepine on the pharmacokinetics of tramadol.

Carbamazepine

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

Cimetidine

With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore no alteration of the Tramadol Capsules dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Quinidine

A study in 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the tramadol C_{max} and AUC; T_{max} is unaffected. However, the increase in C_{max} and AUC fall within the normal therapeutic range for tramadol, and no dosage adjustment is required.

4.6 Pregnancy and lactation

Pregnancy

Animal studies (rats and rabbits, exposure to tramadol up to 7 times that expected in man) have not revealed teratogenic effects and minimal embryo-toxicity (delayed ossification). Fertility, reproductive performance and development of offspring were unaffected. There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore Tramadol capsules should not be used in pregnant women.

Lactation

Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dose given to the mother. Tramadol Capsules should not be administered during breast-feeding.

4.7 Effects on ability to drive and use machines

Tramadol Capsules may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

4.8 Undesirable effects

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

Cardiovascular system disorders:

Uncommon (< 1%): 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 (< 0.1%): bradycardia, increase in blood pressure

Central and peripheral nervous system disorders:

Common (1-10%): headache, muzziness

Rare (< 0.1%): changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions.

Psychiatric disorders:

Rare (< 0.1%): hallucinations, confusion, sleep disturbance and nightmares. Psychic side-effects may occur following administration of tramadol, which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial ability (e.g decision behaviour, perception disorders). Dependence may occur.

Vision disorders:

Rare (< 0.1%): blurred vision

Respiratory system disorders:

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

Gastrointestinal disorders:

Very common (> 10%): nausea

Common (1-10%): vomiting, constipation, diarrhoea, dry mouth

Uncommon (< 1%): retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating)

Skin and appendages disorders:

Common (1-10 %): sweating

Uncommon (< 1 %): dermal reactions (e.g. pruritis, rash, urticaria)

Musculo-Skeletal system disorders:

Rare (< 0.1%): muscle weakness

Liver and biliary system disorders:

In rare cases, increases in liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.

Urinary system disorders:

Rare (< 0.1 %): micturation disorders (difficulty in passing urine and urinary retention)

Body as a whole:

Rare (0.1%): 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.

4.9 Overdose

Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression.

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramadol Capsules with hemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics

ATC Code: N02AX02

Tramadol Capsule is a centrally acting analgesic. It is a non-selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms which may contribute to its analgesic effect are inhibitor of neuronal reuptake of noradrenalines and enhancement of serotonin release.

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%. When ¹⁴C-labelled tramadol was administered to humans, approximately 90% was excreted via the kidneys with the remaining 10% appearing in the faeces.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The half-life of the terminal elimination phase ($t^{1/2\beta}$) was 6.0 + 1.5h in young volunteers. Tramadol pharmacokinetics shows little age dependence in volunteers upto the age of 75 years. In volunteers aged over 75 years, $t^{1/2\beta}$ was 7.0 + 1.6h on oral administration.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15-45 minutes with a mean C_{max} of 280 to 308 mcg/L and T_{max} of 1.6 to 2h.

Tramadol is metabolised 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 appears 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 humans 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 $t^{1/2\beta}$ may be prolonged in impaired hepatic or renal function. In patients with liver cirrhosis

$t_{1/2\beta}$ tramadol was a mean of $13.3 + 4.9h$; in patients with renal insufficiency (creatinine clearance $< 5ml/min$) it was $11.0 + 3.2h$.

5.3 Preclinical safety data

In single and repeat-dose toxicity studies (rodents and dogs) exposure to tramadol 10 times that expected in man is required before toxicity (hepatotoxicity) is observed. Symptoms of toxicity are typical of opioids and include restlessness, ataxia, vomiting, tremor, dyspnoea and convulsions.

Exposure to tramadol ($>$ that expected in man) in lifetime toxicity studies in rodents did not reveal any evidence of carcinogenic hazard, and a battery of in-vitro and in-vivo mutagenicity tests were negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tramadol 50 mg Capsules contain:

Microcrystalline cellulose
Sodium starch glycolate
Silica colloidal anhydrous
Magnesium stearate

The capsule shell contains

Gelatin
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Sodium laurilsulfate
Colours E132, E171 , E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Aluminium/PVDC coated PVC blister packs of 10, 20, 30, 100 capsules.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd.
Unit 3, Canalside, Northbridge Road,
Berkhamsted, Herts, HP4 1EG,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0110

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/06/2006

10 DATE OF REVISION OF THE TEXT

02/09/2006

Patient Information Leaflet

TRAMADOL 50MG CAPSULES

PL 17907/0110

**PATIENT INFORMATION LEAFLET
TRAMADOL 50 mg CAPSULES**

Read all of this leaflet before this medicine is given to you. Even if you have used Tramadol Capsules or a similar product before, you should read this text carefully as the information may have changed.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet :

1. What Tramadol Capsules are and what they are taken for
2. Before you take Tramadol Capsules
3. How to take Tramadol Capsules.
4. Possible side effects
5. Storing Tramadol Capsules
 - The active substance is tramadol hydrochloride
 - Each Tramadol Capsule contains 50 mg tramadol hydrochloride.
 - The other ingredients are microcrystalline cellulose (E460 (I)), sodium starch glycolate, magnesium stearate and silica colloidal anhydrous (inactive ingredients).

The capsule is made of gelatin, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sodium laurilsulfate and colours Indigo carmine (E132), Titanium Dioxide (E171), Yellow Ferric Oxide (E172).

What do they look like?

Tramadol Capsules are green and yellow. They are packed in blister strips and supplied in boxes of 10, 20, 30 or 100 capsules. (Not all pack sizes may be marketed).

Product licence holder and Manufacturer: Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG.

WHAT ARE TRAMADOL CAPSULES AND WHAT ARE THEY USED FOR

Tramadol Capsule is an "analgesic" which acts on central nervous system (the brain and spinal cord). Analgesics are often called "pain killers" or "pain relievers".

Tramadol Capsules relieve pain and can also be taken to prevent pain.

Pain is a symptom not an illness. There are many types of pain with many different causes, for examples backache, toothache, pain after an operation or pain from broken bones.

When part of your body is damaged, inflamed, or put under stress, it releases chemicals, which stimulate your nerve endings. This sets off a relay of electrical impulses and chemical messengers (a pain message), which travel along the nerves and into your brain. When your brain receives the message, you feel pain.

Tramadol Capsules help your body's system for relieving pain. It does this in two ways:

- acts directly on parts of your brain and spinal cord to reduce the amount of pain you feel.
- reduces the size of the pain message passed from one nerve to another.

Tramadol Capsules should only be taken by adults

and by children over 12.

BEFORE YOU TAKE TRAMADOL CAPSULES

DO NOT take Tramadol Capsules:

- You should not take Tramadol Capsules if you are hypersensitive to or have had an allergic reaction, skin rash, swelling of the face, wheezing or difficulty breathing after taking tramadol or any of the other ingredients in Tramadol Capsules.
- If you are pregnant or if you are breast-feeding.
- If you are taking a monoamine oxidase inhibitor (MAOI) or have taken one in the past two weeks. You should know if you are taking an MAOI because your doctor or chemist will have told and you may also have a treatment card.
- If you have drunk enough alcohol to make you feel woozy or drunk.
- If you feel "high" or excited because you have taken medicines that slow the nervous system. These medicines include tranquillisers, sleeping pills, psychotropic medicines (medicines that affect your mood or emotions) and other pain relievers such as morphine and codeine.
- If you have severe kidney disease.

Take special care with Tramadol Capsules

- If you have had a head injury or have brain disease. These can increase the pressure in your skull. If you have a very bad headache or vomit without feeling sick first, it could be a sign of this.
- If you suffer from epilepsy, convulsions or seizures (fits) or have had them in the past.
- If you feel light headed, faint, cold or clammy, or look pale. This could mean you are in a state of 'shock'.
- If you suffer from asthma, other lung disease or have slow or difficult breathing.
- If you suffer from kidney or liver disease.

The excipients propyl parahydroxybenzoate (E216) and methyl parahydroxybenzoate (E218) may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

Taking Tramadol Capsules with food and drink

You should avoid alcohol during treatment with Tramadol Capsules.

Pregnancy

There is very little information regarding the safety of tramadol in human pregnancy therefore Tramadol Capsules should not be used in pregnant women.

Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding

Because tramadol hydrochloride may be harmful to nursing infants, women must stop breast-feeding before starting treatment with Tramadol Capsules.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:

Do not drive or operate any tools or machines if you feel tired or sleepy after treatment with Tramadol Capsules. These effects are made worse if alcohol and/or CNS depressants are taken at the same time.

Taking other medicines:

- Please inform your doctor or pharmacist if you are taking other medicines that have an effect on the nervous system while you

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are taking Tramadol Capsules, you may feel drowsier or feel that you might faint. If this happens tell your doctor. These other medicines include tranquillisers, sleeping pills, antidepressants and other pain relievers such as morphine and codeine.

- if you use alcohol with Tramadol Capsules you may feel drowsier than when taking alcohol alone.
- if you are going to be given a general anaesthetic, tell your doctor or dentist that you are taking Tramadol Capsules.
- if you are taking carbamazepine, a treatment for epilepsy, this may reduce the pain relieving effect of Tramadol Capsules. Your doctor will tell you whether Tramadol Capsules are suitable for you.
- if you are taking antidepressants these may cause convulsions (fits). The chance of having a fit is rare, but if you are also taking Tramadol Capsules, the risk of having a fit may increase. Your doctor will tell you whether Tramadol Capsules are suitable for you.
- if you are taking selective serotonin reuptake inhibitors (often referred to as SSRI's) or triptans, because it has been shown that Tramadol Capsules may interfere with their action by enhancing their effects.
- if you are taking lithium, make sure your doctor or dentist knows. Tramadol Capsules could alter the effect of lithium.
- if you are taking coumarin anticoagulants (bloodthinning medicines), e.g. Warfarin, Tramadol Capsules could alter their effect if taken at the same time.
- if you are taking or have recently taken any other medicines, even those not Prescribed.

HOW TO TAKE TRAMADOL CAPSULES

Follow your doctor's instructions on how many Tramadol Capsules to take and when to take them. You will also find this information on the label. You should usually swallow one or two capsules at a time. Do not take them more often than every four hours and do not take more than eight capsules in any 24 hours unless your doctor tells you to. Swallow the capsules whole, not divided or chewed, with sufficient liquid, and independent of meals. If you are not sure, ask your doctor or pharmacist.

Do not take a different amount of Tramadol Capsules or take it more often than your doctor told you to. These Tramadol Capsules are for you. You must not give them to other people. If you have chronic pain (pain that lasts for long periods of time), it is best to take Tramadol Capsules over short periods and only when you need it.

You can get addicted to some pain relievers. But this is unlikely to happen with Tramadol Capsules as long as you follow your doctor's instructions.

If you take more Tramadol Capsules than you should:

If you take two single doses of Tramadol Capsules at once by mistake, this will generally not be harmful. If pain returns, continue taking Tramadol Capsules as usual.

If high doses are taken accidentally, a number of symptoms may occur. These might include: pin-point pupils, vomiting, a fall in blood pressure, a fast heartbeat, collapse, disturbed consciousness including coma (deep

unconsciousness), epileptic fits, and difficulties breathing. In such cases a doctor should be called immediately.

The capsules should be taken in the packaging to the doctor or casualty unit to allow ready identification.

If you forget to take Tramadol Capsules:

If you forget to take the capsules, pain is likely to return. Do not take a double dose to make up for forgotten individual doses, simply continue taking the capsule as before.

POSSIBLE SIDE EFFECTS

Like all medicines, Tramadol Capsules can have side effects.

- Some people may feel sick, tired, sleepy or dizzy. They may vomit or sweat, become flushed complain of getting a headache, hallucinations, sleep disturbance, nightmares or pins and needles. They may have diarrhoea or constipation or suffer a loss of appetite. These side effects are usually mild and not troublesome.
- Some people's blood pressure drops suddenly, making them feel faint or dizzy, or giving them blurred vision when they get up. Getting up slowly will help to ease this problem. Tell your doctor if this often happens to you.
- Some people may develop itching, a dry mouth, high blood pressure or their heart beat may change. They may feel uneasy, restless, or confused. Tell your doctor if this happens to you.
- Rarely, when some people stop taking Tramadol Capsules they get withdrawal symptoms. They may feel agitated, anxious, nervous or shaky. They may be hyperactive and have difficulty sleeping. These effects usually disappear after a few days. Tell your doctor if this happens to you.
- Rarely some people may get blurred vision or have difficulty passing urine.
- In rare cases, increases in liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.

Contact your doctor immediately if :

- you have difficulty breathing
- your asthma gets worse
- you get an allergic reaction, skin rash, swelling of the face, or wheezing
- you have a fit
- you constantly have a sore throat or high temperature

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING TRAMADOL CAPSULES

Keep out of the reach and sight of children. Keep in a cool, dry place. Do not store above 25°C.

Store in the original package. Do not use your capsules after the expiry date printed on the pack. Return any unused capsules to your pharmacy.

This leaflet was revised in July 2006.

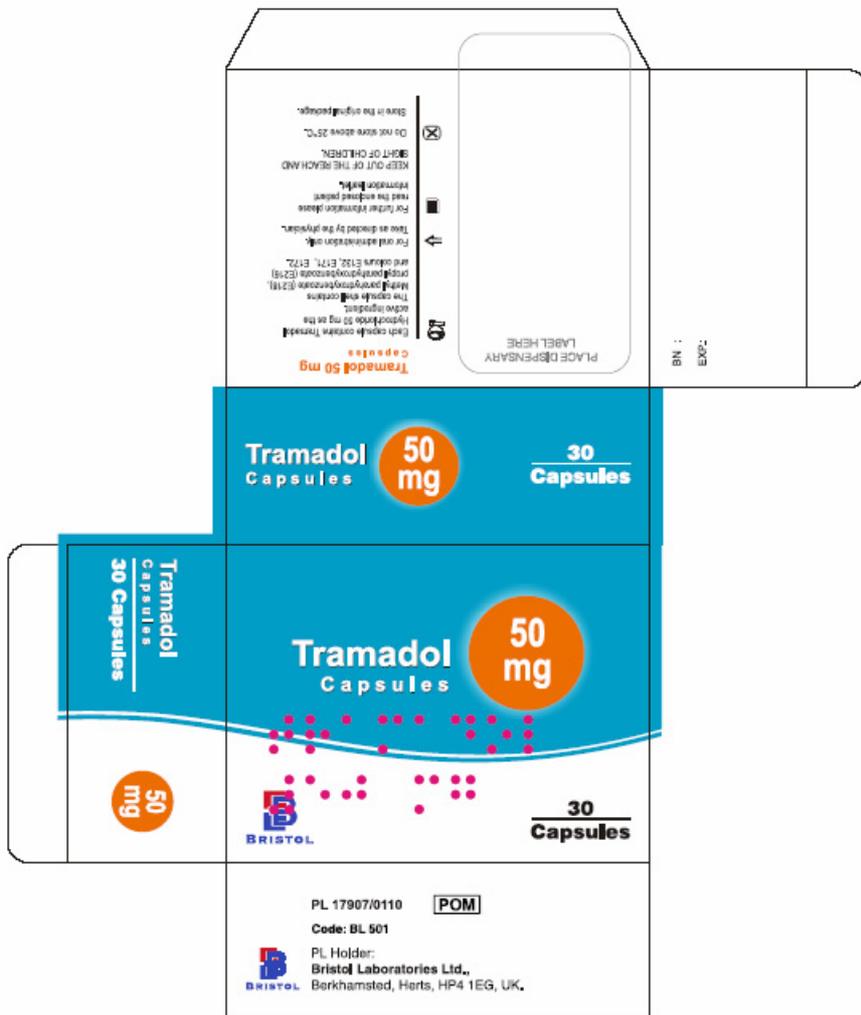
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Labels/Packaging

TRAMADOL 50MG CAPSULES

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