Safeguarding public health

Public Assessment Report

Decentralised Procedure

TRAMADOL HYDROCHLORIDE 50MG/ML SOLUTION FOR INJECTION OR INFUSION

UK/H/3651/001/DC
UK Licence No: PL 25298/0035

BROWN & BURK UK LIMITED

Medicines and Healthcare products Regulatory Agency

LAY SUMMARY

On 25th October 2011, the UK granted Brown & Burk UK Limited a Marketing Authorisation (licence) for the medicine Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion.

Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion contains the active ingredient tramadol hydrochloride. Tramadol hydrochloride is a pain killer 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 Hydrochloride 50mg/ml Solution for Injection or Infusion is used for the treatment of moderate to severe pain.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion
Type of Application	Generic, Article 10.1
Active Substance	Tramadol hydrochloride
Form	50 mg/ml Solution for Injection or Infusion
MA Holder	Brown & Burk UK Limited
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Portugal (PT)
Procedure Number	UK/H/3651/001/DC
End of Procedure	Day 203: 28th September 2011

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 50 mg Tramadol Hydrochloride in 1ml solution or 100 mg Tramadol Hydrochloride in 2ml solution.

Excipient: Each ampoule contains 0.03 mmol (0.7mg) sodium (as acetate trihydrate) in 1ml solution or 0.06 mmol (1.4mg) sodium (as acetate trihydrate) in 2ml solution.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Unless otherwise prescribed, Tramadol Hydrochloride should be administered as follows:

Adults and adolescents above the age of 12 years:

Tramadol Hydrochloride injection may be administered intramuscularly, by slow intravenous injection, or diluted in solution (see Section 6.6) for administration by infusion or patient controlled analgesia.

The usual dose is 50 or 100 mg 4-6 hourly by the intravenous or intramuscular route. Dosage should be adjusted according to pain severity and response.

Intravenous injections must be given slowly over 2-3 minutes.

For post-operative pain administer an initial bolus of 100 mg. During the 60 minutes following the initial bolus, further doses of 50 mg may be given every 10-20 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50 mg or 100 mg 4-6 hourly up to a total daily dose of 600 mg.

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

Children

Tramadol Hydrochloride Solution for Injection is not suitable for children below the age of 12 years.

Geriatric patients

A dose adjustment is not usually necessary in elderly patients (up to 75 years) without clinically manifest hepatic or renal insufficiency. In elderly patients (over 75 years) elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal Insufficiency/Dialysis and Hepatic Insufficiency
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.

4.3 Contraindications
Tramadol Hydrochloride Solution for Injection is contraindicated

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

-in acute intoxication with alcohol, hypnotics, analgesics, opioids, or psychotropic medicinal products,

- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see section 4.5),

- in patients with epilepsy not adequately controlled by treatment,

- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use
Tramadol Hydrochloride 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 (600 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 only be 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 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.

This medicinal product contains less than 1 mmol sodium (23mg) per dose i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction
Tramadol Hydrochloride should 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.

Concomitant administration of Tramadol Hydrochloride SR 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 serotoninergic 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 serotoninergic 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There is inadequate evidence available on the safety of tramadol in human 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. Therefore Tramadol Hydrochloride 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 is 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

Even when taken according to instructions, Tramadol Hydrochloride may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with alcohol and other psychotropic substances.

4.8 Undesirable effects

Rapid intravenous administration may be associated with a higher incidence of adverse effects and therefore should be avoided.

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

Cardiovascular disorders:
uncommon (≥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 (≥1/10000, <1/1000): bradycardia, increase in blood pressure

Nervous system disorders:

very common (≥1/10): dizziness

common (≥1/100, <1/10): headache, somnolence

rare (≥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 (≥1/10000, <1/1000): hallucinations, confusion, sleep disturbance, anxiety and nightmares. Psychic adverse reactions may occur following administration of Tramadol Hydrochloride 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 (≥1/10000, <1/1000): blurred vision
Respiratory disorders:

*rare (≥1/10000, <1/1000):*dyspnoea

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

Gastrointestinal disorders:
very common (≥1/10): nausea

common (≥1/100, <1/10): vomiting, constipation, dry mouth

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

Skin and subcutaneous disorders:
common (≥1/100, <1/10): sweating

*uncommon (≥1/1000, <1/100):*dermal reactions (e.g. pruritus, rash, urticaria)

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

General disorders:
common (≥1/100, <1/10): fatigue

rare (≥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
In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment
The general emergency measures apply. Keep open the respiratory tract (aspiration!), maintain respiration and circulation depending on the symptoms. The stomach is to be emptied by vomiting (conscious patient) or gastric irrigation. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramadol Hydrochloride with haemodialysis or haemo-filtration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids; ATC-code N 02: AX 02.

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and 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

More than 90% of Tramadol Hydrochloride is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

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

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 to 45 minutes within a mean C_{max} of 280 to 208 mcg/L and T_{max} of 1.6 to 2h.

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

Elimination half-life $t_{1/2,\beta}$ is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically

active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life $t_{1/2,\beta}$ (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol.

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. Up to now, clinically relevant interactions have not been reported.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90 % of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 ± 3.2 h and 16.9 ± 3 h, in an extreme case 19.5 h and 43.2 h respectively.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100-- 300 ng/ml is usually effective.

5.3 Preclinical safety data

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dog's 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 dog's 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

sodium acetate trihydrate
water for injection

6.2 Incompatibilities

Precipitation will occur if Tramadol Hydrochloride injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indomethacin, midazolam and piroxicam.

6.3 Shelf life

3 years.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8°C, unless opening/ dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear type I glass ampoules containing either 1ml or 2ml of tramadol hydrochloride solution.

Pack sizes: 1 ampoule per carton, 2 ampoules per carton, 5 ampoules per carton, 10 ampoules per carton and 20 ampoules per carton

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The product should be inspected visually for particles and discoloration prior to administration. Only clear colourless solution free from particles should be used. Do not use the product if there are signs of damage to the ampoule.

Instructions for opening the glass ampoule:
Using a blade, cut the Ampoule at the snap off point, depicted by a green ring (for 1 ml ampoules) or a red ring (for 2 ml ampoules).

After opening the ampoule, the contents should be filtered using a suitable filter device or filter straw prior to use.

Tramadol Hydrochloride solution for injection or infusion is physically and chemically compatible for up to 24 hours with 4.2% sodium bicarbonate and Ringer's solution and for up to 4 days with the following infusion solutions:

0.9% sodium chloride
0.18% sodium chloride and 4% glucose
sodium lactate compound
5% glucose
haemaccel

For single use only. Discard any unused solution.

See section 6.2 for incompatibilities.

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

7 MARKETING AUTHORISATION HOLDER

Brown &Burk UK Ltd.
5 Marryat Close, Hounslow West
Middlesex, TW4 5DQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25298/0035

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/10/2011

10 DATE OF REVISION OF THE TEXT

25/10/2011

Module 3
Product Information Leaflet

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion

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 your 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 your pharmacist.

In this leaflet:

The name of this medicine is Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion (referred to as Tramadol Hydrochloride Injection or Infusion throughout this leaflet).

1. WHAT TRAMADOL HYDROCHLORIDE INJECTION OR INFUSION IS AND WHAT IT IS USED FOR

Tramadol - the active substance in Tramadol Hydrochloride Injection or Infusion - 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 Hydrochloride Injection or Infusion is used for the treatment of moderate to severe pain.

2. BEFORE YOU ARE GIVEN TRAMADOL HYDROCHLORIDE INJECTION OR INFUSION

Do not take Tramadol Hydrochloride Injection or Infusion
- if you are allergic (hypersensitive) to tramadol or any of the other ingredients of Tramadol Hydrochloride Injection or Infusion;
- in acute poisoning with alcohol, sleeping pills, pain relievers or other psychotropic medicines (medicines that affect mood and emotions);
- if you are also taking MAO inhibitors (certain medicines used for treatment of depression) or have taken them in the last 14 days before treatment with Tramadol Hydrochloride Injection or Infusion (see "Taking other medicines");
- 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 Hydrochloride Injection or Infusion
- 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 a tendency towards 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.
- carbamazepine (for epileptic fits);
- pentazocine, nalbuphine or buprenorphine (pain killers);
- ondansetron (prevents nausea).

Your doctor will tell you whether you should take Tramadol Hydrochloride Injection or Infusion, and what dose.
The risk of side effects increases,
- if you take tranquillizers, sleeping pills, other pain relievers such as morphine and codeine (also as cough medicine), and alcohol while you are taking Tramadol Hydrochloride Injection or Infusion. You may feel more drowsy or feel that you might faint. If this happens tell your doctor.
- if you are taking medicines which may cause convulsions (fits), such as certain antidepressants. The risk of having a fit may increase if you take Tramadol Hydrochloride Injection or Infusion at the same time. Your doctor will tell you whether Tramadol Hydrochloride Injection or Infusion is suitable for you.
- if you are taking selective serotonin reuptake inhibitors (often referred to as SSRIs) or MAO inhibitors (for the treatment of depression). Tramadol Hydrochloride Injection or Infusion may interact with these medicines and you may experience symptoms such as confusion, restlessness, fever, sweating, uncoordinated movement of limbs or eyes, uncontrollable jerking of muscles, or diarrhoea.
- if you take coumarin anticoagulants (medicines for blood thinning), e.g. warfarin, together with Tramadol Hydrochloride Injection or Infusion. The effect of these medicines on blood clotting may be affected and bleeding may occur.

Taking Tramadol Hydrochloride Injection or Infusion with food and drink
Do not drink alcohol during treatment with Tramadol Hydrochloride Injection or Infusion as its effects may be intensified.

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 Hydrochloride Injection or Infusion 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 Hydrochloride Injection or Infusion may cause drowsiness, dizziness and blurred vision and therefore may impair your reactions. If you feel that your reactions are affected, do not drive a car or other vehicle, do not use electric tools or operate machinery, and do not work without a firm hold!

3. HOW TRAMADOL HYDROCHLORIDE INJECTION OR INFUSION IS GIVEN

Tramadol Hydrochloride Injection or Infusion should always be used exactly as prescribed by your doctor. 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 used.

Unless otherwise prescribed by your doctor, the usual dose is:
Adults and adolescents from the age of 12 years:
Depending on your pain you will have 1-2 ml of Tramadol Hydrochloride Injection or Infusion (equivalent to 50 – 100 mg Tramadol Hydrochloride) every 4 to 6 hours. After an operation you may need injections more often.
Your doctor may prescribe a different, more appropriate dosage of Tramadol Hydrochloride Injection or Infusion.

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 (600 mg).

Please note that Tramadol Hydrochloride Injection or Infusion may lead to physical and psychological addiction. When Tramadol Hydrochloride Injection or Infusion is 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 Hydrochloride Injection or Infusion 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 Hydrochloride Injection or Infusion treatment or if they applied to you in the past.

Tramadol Hydrochloride Injection or Infusion contains less than 1 mmol sodium (23 mg) per dose, therefore it is essentially 'sodium-free'.

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

Tramadol Hydrochloride Injection or Infusion should not be taken together with MAO inhibitors (certain medicines for the treatment of depression).

The pain-relieving effect of Tramadol Hydrochloride Injection or Infusion may be reduced and the length of time it acts may be shortened, if you take medicines which contain:

Children
Tramadol Hydrochloride Injection or Infusion is 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 direct to prolong the dosage interval.

Liver or kidney disease (insufficiency)/dialysis patients
Patients with severe liver and/or kidney insufficiency should not take Tramadol Hydrochloride Injection or Infusion. If in your case the insufficiency is mild or moderate, your doctor may recommend prolonging the dosage interval.

How and when should you have Tramadol Hydrochloride Injection or Infusion?
Tramadol Hydrochloride Injection or Infusion will be injected slowly usually into a blood vessel under the surface of the arm or injected into muscle (usually the buttocks).
Alternatively, Tramadol Hydrochloride Injection or Infusion will be diluted and infused into a vein.

For medical and healthcare professionals further information on administration is given in a separate leaflet.

How long should you have Tramadol Hydrochloride Injection or Infusion?
You should not have Tramadol Hydrochloride Injection or Infusion 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 have Tramadol Hydrochloride Injection or Infusion and at what dose.

If you have the impression that the effect of Tramadol Hydrochloride Injection or Infusion is too strong or too weak, talk to your doctor or pharmacist.

If you have more Tramadol Hydrochloride Injection or Infusion than you should
If you have had an additional dose by mistake, this will generally have no negative effects. You should have your next dose as prescribed. After very high doses, pin-point pupils, vomiting, fall in blood pressure, fast heart beat, collapse, disturbed consciousness up to coma (deep unconsciousness), epileptic fits, and difficulty in breathing up to cessation of breathing may occur. In such cases a doctor should be called immediately.

If the use of Tramadol Hydrochloride Injection or Infusion has been forgotten
If you do not have your Tramadol Hydrochloride Injection or Infusion or infusion, pain is likely to return. You should not have a double dose to make up for forgotten individual doses; simply continue having Tramadol Hydrochloride Injection or Infusion as before.

If the use of Tramadol Hydrochloride Injection or Infusion is stopped
If treatment with Tramadol Hydrochloride Injection or Infusion is interrupted or finished too soon, pain is likely to return. If you wish to stop treatment on account of unpleasant effects, please tell your nurse or doctor.

Generally there will be no after-effects when treatment with Tramadol Hydrochloride Injection or Infusion is stopped. However, on rare occasions, people who have been treated with Tramadol Hydrochloride Injection or Infusion for some time may feel unwell if the treatment is abruptly stopped. 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 "ringing" in the ears (tinnitus).

If you experience any of these complaints after stopping Tramadol Hydrochloride Injection or Infusion, please tell your nurse or doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tramadol Hydrochloride Injection or Infusion can cause side effects, although not everybody gets them.
In case one of the following situations occurs, 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 Hydrochloride Injection or Infusion 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 Hydrochloride. 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 Hydrochloride 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.
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 HYDROCHLORIDE INJECTION OR INFUSION

Keep out of the reach and sight of children.
Do not use Tramadol Hydrochloride Injection or Infusion after the expiry date which is stated on the carton and the label. The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions.
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 Hydrochloride Injection or Infusion contains
The active substance is tramadol hydrochloride. Each ampoule contains 50 mg Tramadol Hydrochloride in 1ml solution or 100 mg Tramadol Hydrochloride in 2ml solution.
The other ingredients are: sodium acetate trihydrate and water for injections

What Tramadol Hydrochloride Injection or Infusion looks like and contents of the pack
Tramadol Hydrochloride Injection or Infusion is a clear colourless solution supplied in clear glass ampoules. Each ampoule with a green ring contains 1 ml solution and each ampoule with a red ring contains 2 ml solution.
Tramadol Hydrochloride Injection or Infusion is packed as 1 ampoule per carton, 2 ampoules per carton, 5 ampoules per carton, 10 ampoules per carton and 20 ampoules per carton.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Brown & Burk UK Ltd.
5 Marryat Close, Hounslow West
Middlesex, TW4 5DQ
United Kingdom
This leaflet was last approved: 09/2011

The following information is intended for medical or healthcare professionals only:

Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion
Please read this information carefully before using Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion (referred to as Tramadol Hydrochloride Injection or Infusion throughout this leaflet). Further information is available in the Summary of Product Characteristics.

Presentation
The product is presented in clear type I glass ampoules containing either 1ml or 2ml of tramadol hydrochloride solution.
Each 1ml ampoule contains 50 mg tramadol hydrochloride and each 2 ml ampoule contains 100 mg tramadol hydrochloride. Pack sizes include 1 ampoule per carton, 2 ampoules per carton, 5 ampoules per carton, 10 ampoules per carton and 20 ampoules per carton. Not all pack sizes may be marketed.

Indications
Treatment of moderate to severe pain.

Dosage and Method of Administration
The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient.
Unless otherwise prescribed, Tramadol Hydrochloride should be administered as follows:

Adults and adolescents above the age of 12 years:
Tramadol Hydrochloride injection may be administered intramuscularly, by slow intravenous injection, or diluted in solution for administration by infusion or patient controlled analgesia.
The usual dose is 50 or 100 mg 4-6 hourly by the intravenous or intramuscular route. Dosage should be adjusted according to pain severity and response.

Intravenous injections must be given slowly over 2-3 minutes.
For post-operative pain administer an initial bolus of 100 mg. During the 60 minutes following the initial bolus, further doses of 50 mg may be given every 10-20 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50 mg or 100 mg 4-6 hourly up to a total daily dose of 600 mg.

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

Children:
Tramadol Hydrochloride Solution for Injection is not suitable for children below the age of 12 years.

Geriatric patients:
A dose adjustment is not usually necessary in elderly patients (up to 75 years) without clinically manifest hepatic or renal insufficiency. In elderly patients (over 75 years) elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal Insufficiency/Dialysis and Hepatic Insufficiency:
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.

Incompatibilities
Precipitation will occur if Tramadol Hydrochloride injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indomethacin, midazolam and piroxicam.

Shelf life and storage condition
3 years

This medicinal product does not require any special storage conditions.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8°C, unless opening/ dilution has taken place in controlled and validated aseptic conditions.

Special precautions for disposal and other handling
The product should be inspected visually for particles and discoloration prior to administration. Only clear colourless solution free from particles should be used. Do not use the product if there are signs of damage to the ampoule.

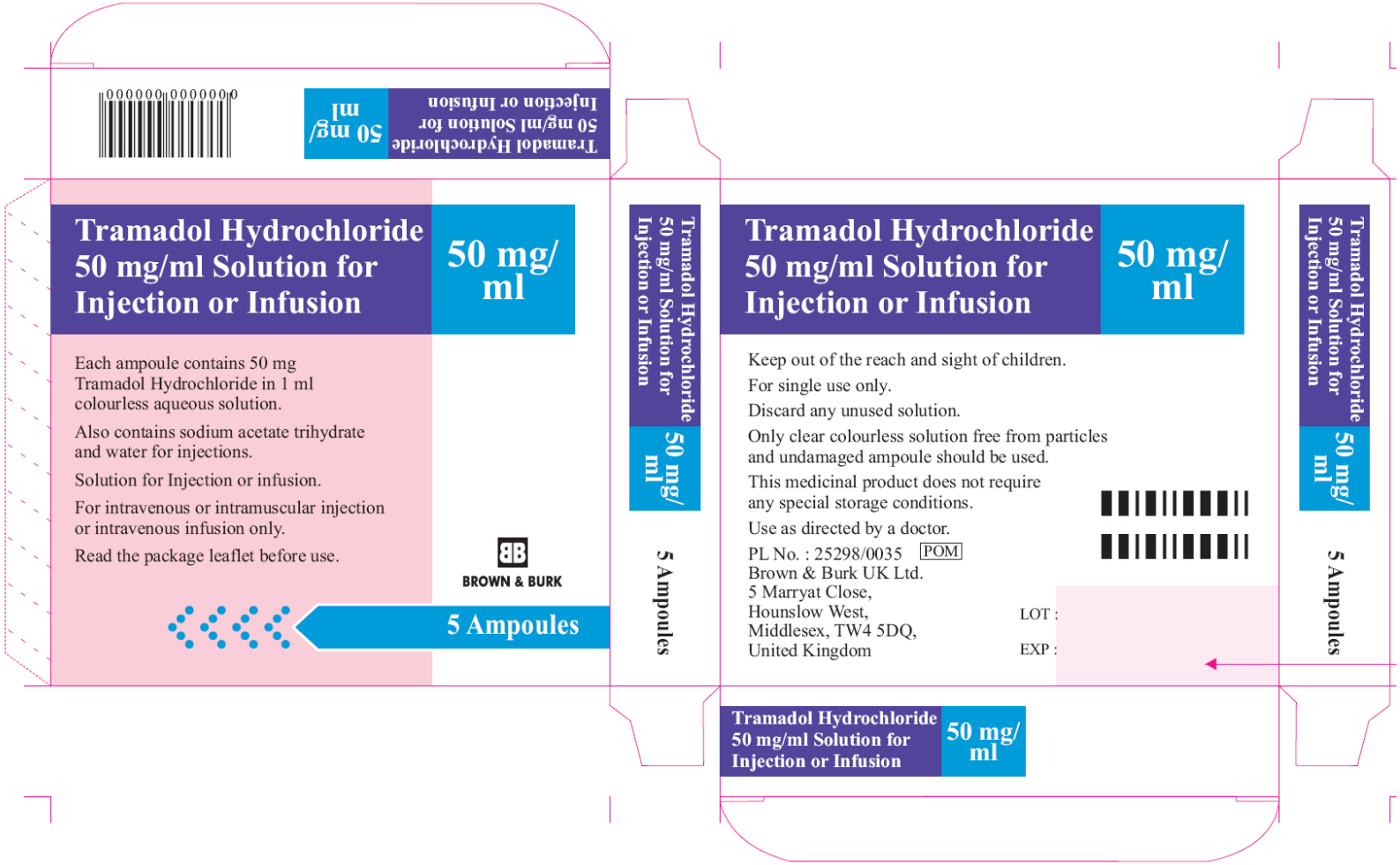
Instructions for opening the glass ampoule:
Using a blade, cut the Ampoule at the snap off point, depicted by a green ring (for 1 ml ampoules) or a red ring (for 2 ml ampoules).
After opening the ampoule, the contents should be filtered using a suitable filter device or filter straw prior to use.

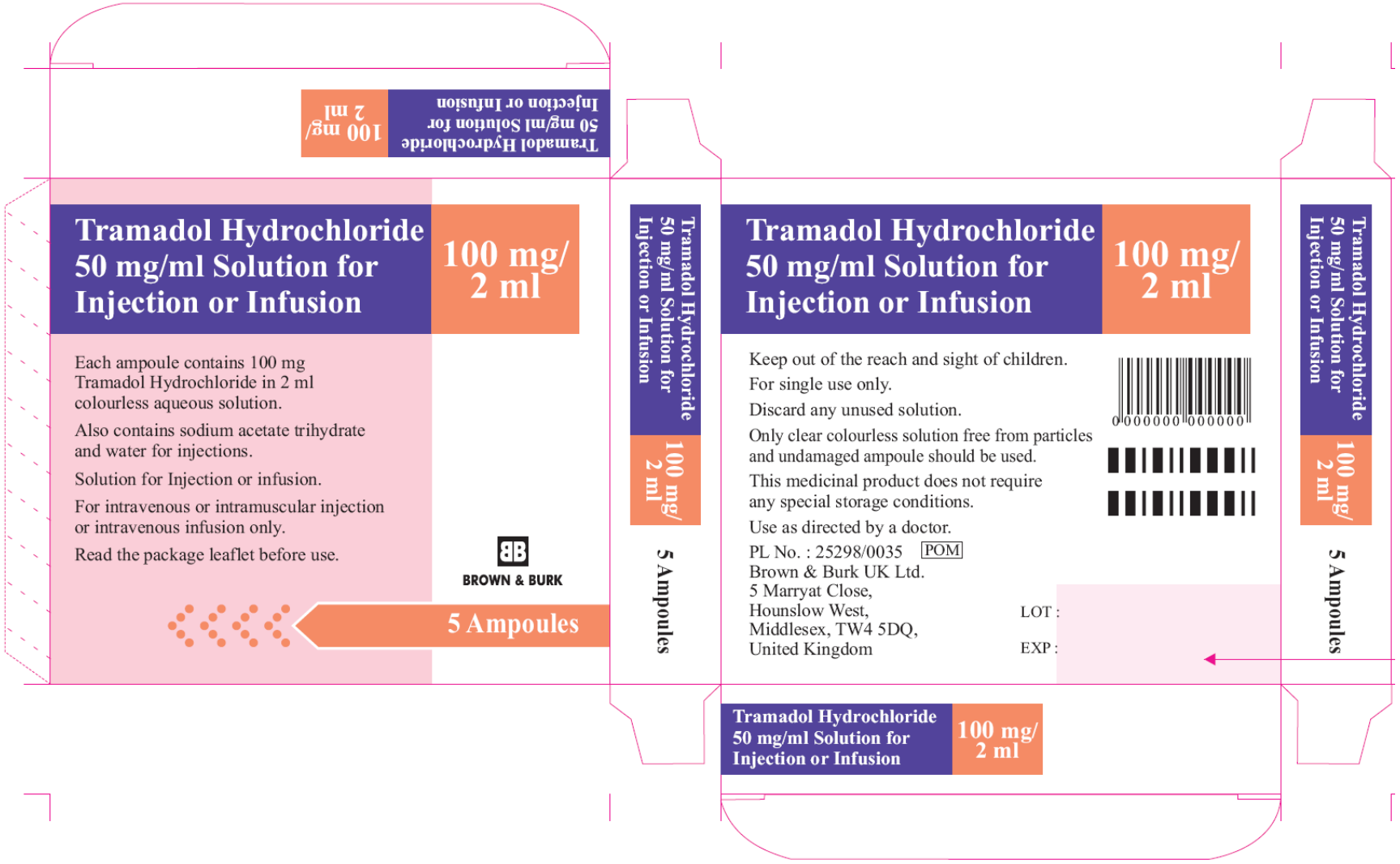
Tramadol Hydrochloride solution for injection or infusion is physically and chemically compatible for up to 24 hours with 4.2% sodium bicarbonate and Ringer's solution and for up to 4 days with the following infusion solutions:
0.9% sodium chloride
0.18% sodium chloride and 4% glucose
sodium lactate compound
5% glucose
haemaccel

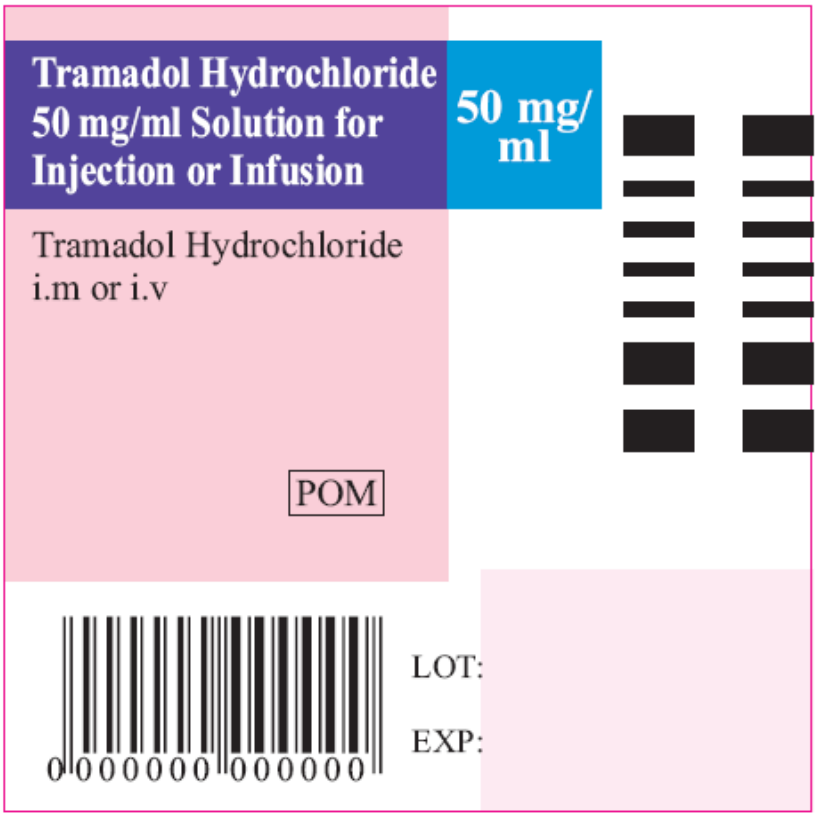
For single use only. Discard any unused solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

Last revision: 09/2011

Module 4
Labelling




Tramadol Hydrochloride 50 mg/ml Solution for Injection or Infusion
100 mg/ 2 ml
Tramadol Hydrochloride 50 mg/ml Solution for Injection or Infusion
100 mg/ 2 ml
Each ampoule contains 100 mg Tramadol Hydrochloride in 2 ml colourless aqueous solution.
Also contains sodium acetate trihydrate and water for injections.
Solution for Injection or infusion.
For intravenous or intramuscular injection or intravenous infusion only.
Read the package leaflet before use.
BROWN & BURK
5 Ampoules
5 Ampoules
Tramadol Hydrochloride 50 mg/ml Solution for Injection or Infusion
100 mg/ 2 ml
Keep out of the reach and sight of children.
For single use only.
Discard any unused solution.
Only clear colourless solution free from particles and undamaged ampoule should be used.
This medicinal product does not require any special storage conditions.
Use as directed by a doctor.
PL No. : 25298/0035 POM
Brown & Burk UK Ltd.
5 Marryat Close,
Hounslow West,
Middlesex, TW4 5DQ,
United Kingdom
LOT :
EXP :
Tramadol Hydrochloride 50 mg/ml Solution for Injection or Infusion
100 mg/ 2 ml
Tramadol Hydrochloride 50 mg/ml Solution for Injection or Infusion
100 mg/ 2 ml
5 Ampoules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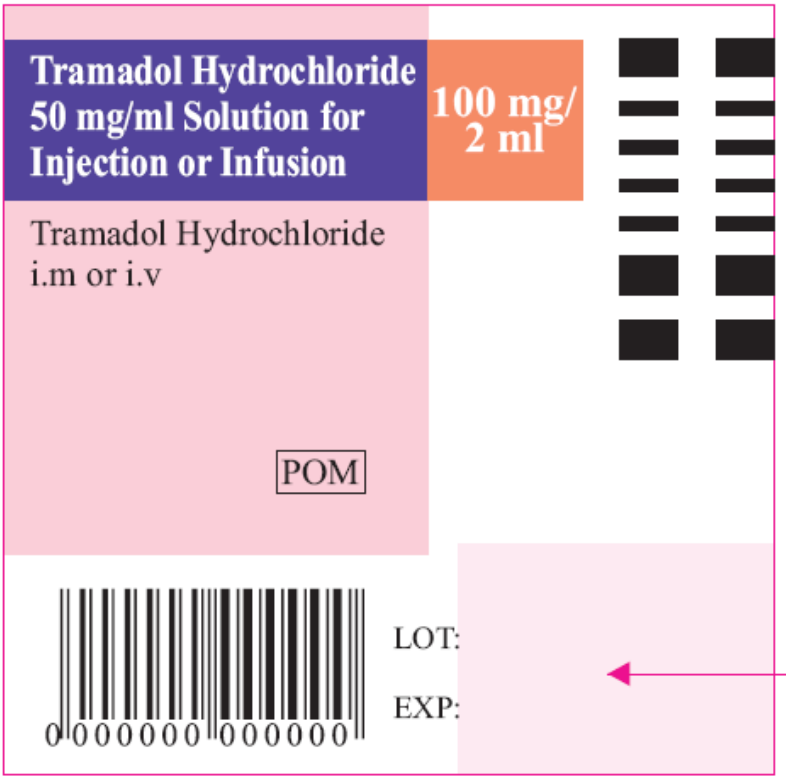
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Tramadol Hydrochloride i.m or i.v
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Portugal and the UK considered that the application for Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion could be approved. The product is a prescription only medicine (POM) and is indicated for moderate to severe pain.

This application for Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Zydol 50ml/ml Solution for Injection, first authorised to G D Searle and Company Limited on 17th November 1994 (PL 00020/0195). This licence then underwent changes of ownership to Monsanto PLC on 7th February 1996 (PL 08821/0004) and Grunenthal Limited on 1st December 2004 (PL 21727/0002).

Tramadol is a centrally-acting, synthetic analgesic with a dual mechanism of weak opioid and monoaminergic effects. It is a racemic mixture and its mechanism of action via opioid and noradrenergic/serotonergic mechanisms is related to the independent effects of its two enantiomers.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. The pharmacology of tramadol hydrochloride is well-established.

No clinical studies have been performed and none are required for this application as the proposed product is an aqueous solution at the time of administration and contains the same concentration of active substance as the already approved reference product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that 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.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

II. ABOUT THE PRODUCT

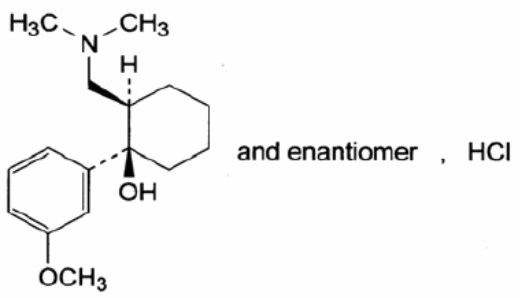
Name of the product in the Reference Member State	Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion
Name(s) of the active substance(s) (INN)	Tramadol hydrochloride
Pharmacotherapeutic classification (ATC code)	Other opioids (N 02 AX 02)
Pharmaceutical form and strength(s)	50 mg/ml Solution for Injection or Infusion
Reference numbers for the Decentralised Procedure	UK/H/3651/001/DC
Reference Member State (RMS)	United Kingdom
Member States concerned (CMS)	Portugal (PT)
Marketing Authorisation Number(s)	PL 25298/0035
Name and address of the authorisation holder	Brown &Burk UK Ltd. 5 Marryat Close, Hounslow West Middlesex, TW4 5DQ United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Tramadol hydrochloride
Chemical name: (1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride
Structural formula:



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

Appearance: White crystalline powder
Solubility: freely soluble in water and in methanol but only very slightly soluble in acetone

Molecular weight: 299.8

Tramadol hydrochloride complies with the European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance from its starting materials are controlled by a Certificate of Suitability.

All potential known impurities and residual solvents have been identified and characterised.

An appropriate specification with suitable test methods and limits is provided for the active substance. The methods of testing and limits for residual solvents are in compliance with current guidelines. Suitable Certificates of Analysis have been provided for all reference standards used. Batch analysis data are provided and comply with the proposed specification.

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

Stability studies have been performed with the active substance and no significant changes of the parameters were observed. On the basis of the results, the RMS agreed that a suitable re-test period could be approved.

P. Medicinal Product

Other Ingredients

Other ingredients are the pharmaceutical excipients sodium acetate trihydrate and water for injections.

Both of the excipients comply with their European Pharmacopoeia monographs.

Neither of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to produce a safe, efficacious product containing tramadol hydrochloride that could be considered a generic medicinal product of Zydol 50ml/ml Solution for Injection.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative *in vitro* impurity profiles have been provided for the proposed and reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches have been provided and are satisfactory. The applicant has committed to perform process validation on future production-scale batches.

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

Container-Closure System
This product is packaged in clear type I glass ampoules containing either 1ml or 2ml of tramadol hydrochloride solution.

The product comes in the following pack sizes: 1 ampoule per carton, 2 ampoules per carton, 5 ampoules per carton, 10 ampoules per carton and 20 ampoules per carton.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with European Pharmacopoeia regulations.

Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years for an unopened ampoule with no special storage instructions.

From a microbiological point of view, once opened/diluted, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless opening/dilution has taken place in controlled and validated aseptic conditions.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. The UK approved PIL and label mock-ups are included in modules 3 and 4 of this report.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL 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 form
The MAA form is pharmaceutically satisfactory.

Overall Summary
The pharmaceutical overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of tramadol hydrochloride are well-known. As this is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required. An overview based on literature is thus, appropriate.

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.

A satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.

III.3 CLINICAL ASPECTS

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

CLINICAL PHARMACOLOGY

The applicant's product is a generic product of the reference product; both products contain the same quantitative and qualitative composition of the active ingredient. As per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1, no new pharmacokinetic or pharmacodynamic data were submitted with this generic application and none were required. The test and reference products are identical at the point of administration. Therefore, a human bioavailability study is not required for this application.

EFFICACY

No new efficacy data were submitted with this application and none were required.

SAFETY

No new safety data were submitted with this application and none were required.

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

The SmPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL OVERVIEW

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

MAA FORM

The MAA Form is clinically satisfactory.

CONCLUSIONS

It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Tramadol Hydrochloride 50mg/ml Solution for Injection or Infusion 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 and none are required for applications of this type.

EFFICACY

No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tramadol chloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome