Public Assessment Report

Tramadol Hydrochloride 50mg Orodispersible Tablets

Tramadol Hydrochloride

PL 25124/0001

Pharmaceutical Works Polpharma SA

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Lay Summary

The MHRA granted a marketing authorisation (licence) for the medicinal product Tramadol Hydrochloride 50mg Orodispersible Tablets on 18th December 2007 to Pharmaceutical Works Polpharma SA. This is a prescription only medicine.

Tramadol Hydrochloride 50mg Orodispersible Tablets are used in the treatment and prevention of moderate to severe pain. Tramadol Hydrochloride 50mg Orodispersible Tablets were shown to be identical to the reference product, Zydol 50mg capsules.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Tramadol Hydrochloride 50mg Orodispersible Tablets outweigh the risks, hence a marketing authorisation has been granted.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal product Tramadol Hydrochloride 50mg Orodispersible Tablets (PL 25124/0001) on 18th December 2007. This is a prescription only medicine.

This was a national standard abridged application. The applicant successfully claimed that Tramadol Hydrochloride 50mg Orodispersible Tablets were a generic medical product of PL 21727/0001 Zydol 50mg capsules, granted 30/11/2004, currently marketed by Grunenthal.

This application is a duplicate of PL 06934/0071 Tramelene Flashtab 50mg orodispersible tablets, granted 30/09/2003 and marketed by Ethypharm. Therefore, this application did not contain any Quality information.

PHARMACEUTICAL ASSESSMENT

No quality data were provided for this application and none were required.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

No pre-clinical data were provided for this application and none were required.

MEDICAL ASSESSMENT

Clinical Pharmacology

Tramadol is indicated in the management (treatment and prevention) of moderate to severe pain. Tramadol Hydrochloride 50mg orodispersible tablets are 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 noradrenaline and enhancement of serotonin release.

Bioequivalence study

Single centre, randomised, two-period, cross-over, bioequivalence study of Tramadol 50mg Flashtabs (Ethypharm SA, France) versus Topalgic 50mg capsules (Aventis, France) in healthy male volunteers

Study protocol

Twenty healthy male volunteers aged 18-33 years, were included in this study. 19 subjects were analysed in the pharmacokinetic evaluation of tramadol, and 14 for O-Desmethyltramadol had more than one data higher than the limit of quantitation for both periods. Each subject received a single dose (50mg flashtab or capsule) of one of the two tramadol formulations. For each subject there were 2 dosing periods, with a washout period of 7 days. A randomisation scheme was included in the report.

The reference is registered in UK. The tablet was administered with 200 ml water following a >10hr fast. Standard meals were served at 4 and 11.5h post-dose. Subjects were free to drink additional supplied water 4 h post-dose. Blood samples were taken at pre-dose and at 0.66, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 11, 12, 13, 14 and 24 hours after administration of the products.

Plasma samples were analysed for tramadol and o-desmethyltramadol. The limit of quantitation was 15.06 ng/ml and 13.09ng/ml for tramadol and o-desmethyltramadol respectively**.** The method was validated and the validation report was provided.

$AUC_{(0\text{-}t.)}$, $AUC_{(0\text{-}inf)}$, C_{max}, t_{max} and $t_{½}$ were calculated according normal standard procedures. Statistical evaluation was performed for $AUC_{(0\text{-}t)}$, AUC_{inf} and C_{max} with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

The study was conducted in accordance with GCP and GLP. The report is of good quality.

Results

According to the protocol, subjects 1, 3 – 20 and 2, 5-8, 10-14, 17-20 were included in the analysis of tramadol and o-desmethyltramadol respectively.

Tramadol and O-desmethyltramadol:

Used test for the statistical comparison	Tmax	$t_{1/2z}$	Cmax	AUC_{0-t}	$AUC_{0-\infty}$
Friedman test ($\chi 2$)	N.S.	-	-	-	-
ANOVA					
Treatment	-	N.S.	N.S.	S.($p<0.05$)	S.($p<0.05$)
Subject		S.($p<0.001$)	S.($p<0.001$)	S.($p<0.001$)	S. ($p<0.001$)
Period		N.S.	N.S.	S.($p<0.05$)	N.S.
Power of the study		-	0.983	>0.999	>0.999
Bioequivalence test	-				
① 90% standard confidence interval		① [1.00 – 1.13]	① [0.94 - 1.10]	① [1.04 - 1.12]	① [1.04 - 1.12]
② Two one-sided T-tests (Schuirmann)			can conclude equivalence	② can conclude equivalence	② can conclude equivalence
③ Geometric mean ratio T/R			③ 1.02	③ 1.08	③ 1.08

Used test for the statistical comparison	Tmax	Cmax	AUC_{0-t}
Friedman test ($\chi 2$)	N.S.	-	-
ANOVA (latin square design)			
Treatment	-	N.S.	N.S.
Subject		S.($p<0.001$)	S. ($p<0.001$)
Period		N.S.	N.S.
Power of the study		>0.999	0.966
Bioequivalence test	-		
① 90% standard confidence interval		① [0.94 - 1.06]	① [0.88 – 1.08]
② Two one-sided T-tests (Schuirmann)		② can conclude equivalence	② can conclude equivalence
③ Geometric mean ratio T/R		③ 1.00	③ 0.97

The claim that bioequivalence has been demonstrated was supported.

Efficacy

Efficacy is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

Safety

Safety is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

Expert Report

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

Summary of Product Characteristics

This is satisfactory

Patient Information Leaflet

This is satisfactory

Conclusions

A marketing authorisation was granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

No quality data were submitted for this duplicate application and none were required.

Pre-Clinical

No pre-clinical data were submitted for this application and none were required.

Clinical

Bioequivalence has been demonstrated between the applicant's Tramadol Hydrochloride 50mg Orodispersible Tablets and the reference product.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Zydol tablets.

Risk/Benefit Analysis

The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 5th May 2006.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 3rd August 2006.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 5th February 2007 and 14th June 2007 and on the medical assessment on 14th December 2006.
4	The applicant provided further information in regard to the quality assessment on 20th April 2007, 10th July 2007 and 18th September 2007 and on the medical assessment on 23rd March 2007.
5	The application was determined on 18th December 2007.

Steps Taken after Assessment

None.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tramadol Hydrochloride 50 mg orodispersible tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of tramadol hydrochloride.
Also contains 20mg aspartame.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablets.

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 Hydrochloride 50mg orodispersible tablets 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 toclinical 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 special precautions for use). A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

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 impairment/renal dialysis:
The elimination of tramadol may be prolonged. The usual initial dosage should be used. For patients with creatinine clearance < 30 ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance < 10 ml/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.

The tablet disperses rapidly in the mouth and is then swallowed. Alternatively, the tablet can be dispersed in half a glass of water, stirred and drunk immediately independently of meals.

4.3 Contraindications

Tramadol Hydrochloride 50mg orodispersible tablets should not be administered to patients who have previously demonstrated hypersensitivity to it 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. Tramadol must not be administered during breastfeeding if long term treatment, i.e. more than 2 to 3 days, is necessary (section 4.6)

4.4 Special warnings and precautions for use

Warnings:

At therapeutic doses, Tramadol Hydrochloride 50mg orodispersible tablets has 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 Hydrochloride 50mg orodispersible tablets is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, it cannot suppress morphine withdrawal symptoms.

Precautions:

Tramadol Hydrochloride 50mg orodispersible tablets 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 Interaction 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) anaesthetic technique (with only intermittent administration of enflurane ‘as required’), tramadol was reported to enhance intra-operative recall. Hence its use during potentially very light planes of general anaesthesia should be avoided.

Two recent studies of tramadol administration during anaesthesia comprising continuous administration of isoflurane did not show clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agents is followed, Ethypharm Tramadol Flashtab 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

Concomitant administration of Tramadol Hydrochloride 50mg orodispersible tablets with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore no alteration of the Tramadol Hydrochloride 50mg orodispersible tablets regimen is recommended for patients receiving chronic cimetidine therapy.

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.

Tramadol may increase the potential for both selective serotonin reuptake inhibitors
(SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions (see sections 4.4
Special warnings and special 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.

The analgesic effect of tramadol is in part mediated by inhibition of the re-uptake of norepinephrine and enhancement of the release of serotonin (5-HT). In studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirements of tramadol in patients with postoperative pain.

4.6 Pregnancy and lactation

Pregnancy:

Animal studies (rats and rabbits, exposure to tramadol up to 7 times that expected in man) have revealed no teratogenic effects and minimal embryotoxicity (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 Hydrochloride 50mg orodispersible tablets should not be used in pregnant woman.
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. A single administration of tramadol does not usually require breastfeeding to be interrupted. If repeated administration is needed for several days i.e. more than 2 to 3 days, breastfeeding should be suspended Tramadol Hydrochloride 50mg orodispersible tablets should not be administered during breast feeding if long term treatment is necessary.

4.7 Effects on ability to drive and use machines

Tramadol Hydrochloride 50mg orodispersible tablets 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

Gastrointestinal system:

Nausea, vomiting and occasionally dry mouth. Both diarrhoea and constipation have been reported. In controlled trials the incidence of constipation is lower than that of comparator agents.

Central nervous system and psychiatric:

Tiredness, fatigue, drowsiness, somnolence, dizziness, headache, confusion, hallucinations and infrequently respiratory depression. Dependence, dysphoria and convulsions have been reported rarely (see section 4.5 Interactions).

Physical dependence:

Dependence, abuse and withdrawal reactions have been reported. Typical opiate withdrawal reactions include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms (see sections 4.4 Special warnings and special precatuions for use and 4.2 Posology and method of administration).

Allergic/anaphylactoid reaction:

Dyspnoca, wheezing, broncho spasm and worsening of existing asthma.

Other adverse events:

Diaphoresis, urticaria and pruritus have been reported. Skin rashes, tachycardia, orthostatic hypotension, increase in blood pressure, bradycardia, flushing, syncope and anaphylaxis have been rarely reported. Cases of blood dyscrasias have been rarely observed during treatment with tramadol, but causality has not been established.

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 Hydrochloride 50mg orodispersible tablets with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tramadol Hydrochloride 50mg orodispersible tablets 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 noradrenaline and enhancement of serotonin release.

5.2 Pharmacokinetic properties

The half-life of the terminal elimination phase (t ½ c) was 6.0 ± 1.5 hours in young volunteers. Tramadol pharmacokinetics show little age dependence in volunteeers up to the age of 75 years. In volunteers aged over 75 years, t ½ c was 7.0 ± 1.6 hours on oral administration.
Since tramadol is eliminated both metabolically and renally, the terminal half-life
t ½ c may be prolonged in impaired hepatic or renal function. However, the increase in the t ½ c values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t ½ c tramadol was a mean of 13.3 ± 4.9 hours; in patients with renal insufficiency (creatinine clearance ä 5 ml/min) it was 11.0 ± 3.2 hours.

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 (ä 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

ethylcellulose N7,
copovidone,
colloidal hydrated silica,
mannitol (E421),
crospovidone,
aspartame (E951),
mint rootbeer flavouring,
magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

Polyamide/aluminium/poly(vinylchloride) and aluminium blister packs
Boxes of 10, 20, 28, 30, 40, 50, 56, 60 and 100 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmaceutical Works POLPHARMA S.A.
19, Pelplińska Str., 83-200 Starogard Gdański,
Poland

8 MARKETING AUTHORISATION NUMBER(S)

PL 25124/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/12/2007

10 DATE OF REVISION OF THE TEXT

18/12/2007

Labels and Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

polpharma

Tramadol Hydrochloride 50 mg orodispersible tablets

Tramadol hydrochloride

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

In this leaflet:

The name of this medicine is Tramadol Hydrochloride 50 mg orodispersible tablets. For convenience this leaflet will call it Tramadol tablets.

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

Tramadol tablets are an «analgesic» which acts on the central nervous system (the brain and spinal cord).

Analgesics are often called "pain killers" or "pain relievers".

Tramadol tablets relieve pain and can also be taken to prevent pain. **You may use Tramadol tablets for moderate to severe pain.**

2. BEFORE YOU TAKE TRAMADOL TABLETS

Do not take Tramadol tablets
- if you are **allergic**, to tramadol or any of the other ingredients of the medicine.
- if you are **pregnant** or if you are **breast-feeding**.
- if you are taking a **monoamine oxidase inhibitor** (MAOI used to treat depression) or have taken one in the past two weeks. You should know if you are taking an MAOI because your doctor or pharmacist will have told you 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 slowly affect the nervous system. These medicines include tranquillisers, sleeping pills and other pain relievers such as morphine and codeine.

Tramadol tablets should only be taken by adults and by children over 12.

Take special care with Tramadol tablets
Please tell your doctor if you:
- have had a **head injury** or do you have a **brain disease**. These can increase pressure in your skull. If you have a very bad headache or vomit without feeling sick first, it could be a sign of this.
- suffer from **kidney** or **liver disease.**
- suffer **from epilepsy**, **convulsions** or **seizures** (fits) or have you had them in the past.
- feel **light-headed**, **faint**, **cold** or **clammy**, or **look pale**. This could mean you are in shock.
- suffer from **asthma**, other **lung disease** or have slow or troubled breathing.

Taking other medicines
Make sure that your doctor or dentist knows that you are taking other medicines, including medicines obtained without a prescription.

If you are taking other medicines that affect the **nervous system** while you are taking Tramadol tablets, you may feel more drowsy or feel that you might faint.

Please tell your doctor if you are taking:
- tranquillisers.
- sleeping pills.
- general anaesthetics.
- antidepressants (including those called tricyclic antidepressants and SSRIs) which may cause convulsions (fits). The chance of having a fit is rare, but if you are also taking this medicine , the risk of having a fit may increase.
- other pain relievers such as morphine and codeine.
- lithium (also used to treat some forms of depression). Tramadol tablets could alter the effect of lithium.
- carbamazepine (used to treat epilepsy) may reduce the pain-relieving effect of tramadol.

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

Taking Tramadol tablets with food and drink
Tramadol tablets may make you feel sleepy. As alcohol may also make you feel sleepy, it is best not to drink alcohol when you are taking Tramadol tablets.

Pregnancy and breast-feeding
You should not take Tramadol tablets if you are pregnant, think you may be pregnant or are breast-feeding. **Ask your doctor or pharmacist for advice before taking any medicine.**

Driving and using machines
Do not drive or operate machinery or any other activities which require concentration until you know how Tramadol tablets affect you.

Important information about some of the ingredients of Tramadol tablets
This medicine contains **aspartame,** a source of phenylalanine, which may be harmful for people with **phenylketonuria** (a genetic disorder that is characterized by an inability of the body to utilize the essential amino acid, phenylalanine).

3. HOW TO TAKE TRAMADOL TABLETS

Always take Tramadol tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Tramadol tablets should only be taken by adults and by children over 12.

Instructions for proper use:

Place the tablet in your mouth. It will dissolve directly and quickly in your mouth, so that it can be easily swallowed. You can also place the tablet in a full/half glass of water and stir. Drink it straight away.

You should usually take one or two tablets at a time.
Do not take them more often than every four hours and do not take more than eight tablets in any 24 hours unless your doctor tells you to. If you are not sure, ask your doctor or pharmacist.

If you have chronic pain (pain that lasts for long periods of time), you should check regularly with your doctor that it is appropriate for you to continue taking tramadol.

If you take more Tramadol tablets than you should
If you take more Tramadol tablets than you should, or someone else takes the tablets, then you should contact your nearest hospital or tell your doctor immediately.

After taking 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 breathing up to stoppage of breathing may occur. In such cases a doctor should be called immediately!

If you forget to take Tramadol tablets
If you forget to take your tablets, take them as soon as you remember and carry on with the next dose as usual. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Tramadol tablets
If you interrupt or finish treatment with tramadol too soon, pain may return. If you wish to stop treatment on account of unpleasant side-effects, please consult your doctor.

Generally, there will be no after-effects when treatment with tramadol is stopped. However, when some people stop taking tramadol they get **withdrawal symptoms**. They may feel agitated, anxious, nervous or shaky. They may be hyperactive, have difficulty sleeping and experience stomach or bowel disorders.
These effects usually disappear after a few days.

If you experience any of these side complaints after stopping Tramadol tablets, please consult your 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 tablets can cause side effects, although not everybody gets them.

These effects may be serious, stop taking Tramadol tablets and tell your doctor straight away if they happen to you:
- have difficulty breathing,
- your asthma is getting worse,
- have an allergic reaction (sweating, itchy rash, itching, narrowing of airways, fainting),
- skin rash, swelling of the face or wheezing,
- a fit,
- a constantly sore throat or high temperature,
- mouth ulcers that do not heal rapidly,
- unexplained bruising or bleeding.

Other side effects may also include:
- feeling or being sick, dry mouth,
- diarrhea or constipation,
- tiredness, fatigue,
- drowsiness, sleepiness,
- dizziness, headache,
- confusion, hallucinations (sensing things that are not real),
- abuse and withdrawal symptoms (see also section 3. How to take Tramadol tablets - If you stop taking Tramadol tablets),
- false sense of uneasiness (dysphoria) and fits,
- fast or slow heart beat,
- dizziness on standing up due to low blood pressure, high blood pressure, flushing.

Changes in numbers and types of blood cells (detected by blood test) have been reported in patients taken tramadol but it is not clear if this effect was caused by the medicine.

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 TABLETS

Keep out of the reach and sight of children.

Store in the original package.

Do not use Tramadol tablets after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION

What Tramadol tablets contain
- The active substance is tramadol hydrochloride. Each tablet contains 50 mg tramadol hydrochloride.
- The other ingredients are ethylcellulose N7, copovidone, colloidal hydrated silica, mannitol (E421), crospovidone, aspartame (E951), mint rootbeer flavouring, magnesium stearate.

What Tramadol tablets look like and contents of the pack

Tramadol tablets are round, white, biconcave tablet, engraved 'T' on one side and '50' on the other side, with a characteristic mint flavour.

Tramadol tablets come in packs containing 10, 20 or 30 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorization Holder
Pharmaceutical Works POLPHARMA SA
19 Pelplińska Street, 83-200 Starogard Gdański
POLAND

Manufacturers

ETHYPHARM INDUSTRIES Z.I. de Saint-Arnoult 28170 Chateauneuf-en-Thymerais FRANCE	Pharmaceutical Works POLPHARMA SA 19 Pelplińska Street 83-200 Starogard Gdański POLAND

This leaflet was last approved in


ADHESIVE
POM
PL 25124/0001
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Read the information leaflet carefully before you start to take your medicine. Store in the original package.
Place tablet on tongue and allow to disperse in mouth before swallowing. Take as directed by your doctor.
For oral use: You should not swallow TRAMADOL tablets. Tablets should be sucked, not chewed, as they will dissolve on your tongue. If necessary you may also dissolve each tablet in half a glass of water. Do not chew. Do not swallow whole.
Tramadol Hydrochloride 50 mg orodispersible tablets
The Marketing Authorisation holder is:
Pharmaceutical Works POLPHARMA SA
19 Pelplińska Street, 83-200 Starogard Gdański
Poland
EAN
polpharma
Batch no.
Use by
Tramadol Hydrochloride 50 mg orodispersible tablets
polpharma
10 tablets
Tramadol Hydrochloride 50 mg orodispersible tablets
Tramadol hydrochloride
Tramadol Hydrochloride 50 mg orodispersible tablets
Tramadol Hydrochloride 50 mg orodispersible tablets
Orodispersible tablet containing 50 mg of Tramadol Hydrochloride
INGREDIENTS: Active substance: tramadol hydrochloride. Contains aspartame.
Braille inscriptions
on the front side of the box
TRAMADOL HYDROCHLORIDE
50 MG
ORODISPERSIBLE TABLETS


ADHESIVE
EAN
polpharma
Tramadol Hydrochloride 50 mg orodispersible tablets
Tramadol Hydrochloride 50 mg orodispersible tablets
20 tablets
Tramadol Hydrochloride 50 mg orodispersible tablets
Tramadol hydrochloride
Tramadol Hydrochloride 50 mg orodispersible tablets
Orodispersible tablet containing 50 mg of Tramadol Hydrochloride
INGREDIENTS: Active substance: tramadol hydrochloride. Contains aspartame.
Tramadol Hydrochloride 50 mg orodispersible tablets
Braille inscriptions on the front side of the box


ADHESIVE
EAN
polpharma
Tramadol Hydrochloride 50 mg orodispersible tablets
Tramadol Hydrochloride 50 mg orodispersible tablets
30 tablets
Tramadol Hydrochloride 50 mg orodispersible tablets
Tramadol hydrochloride
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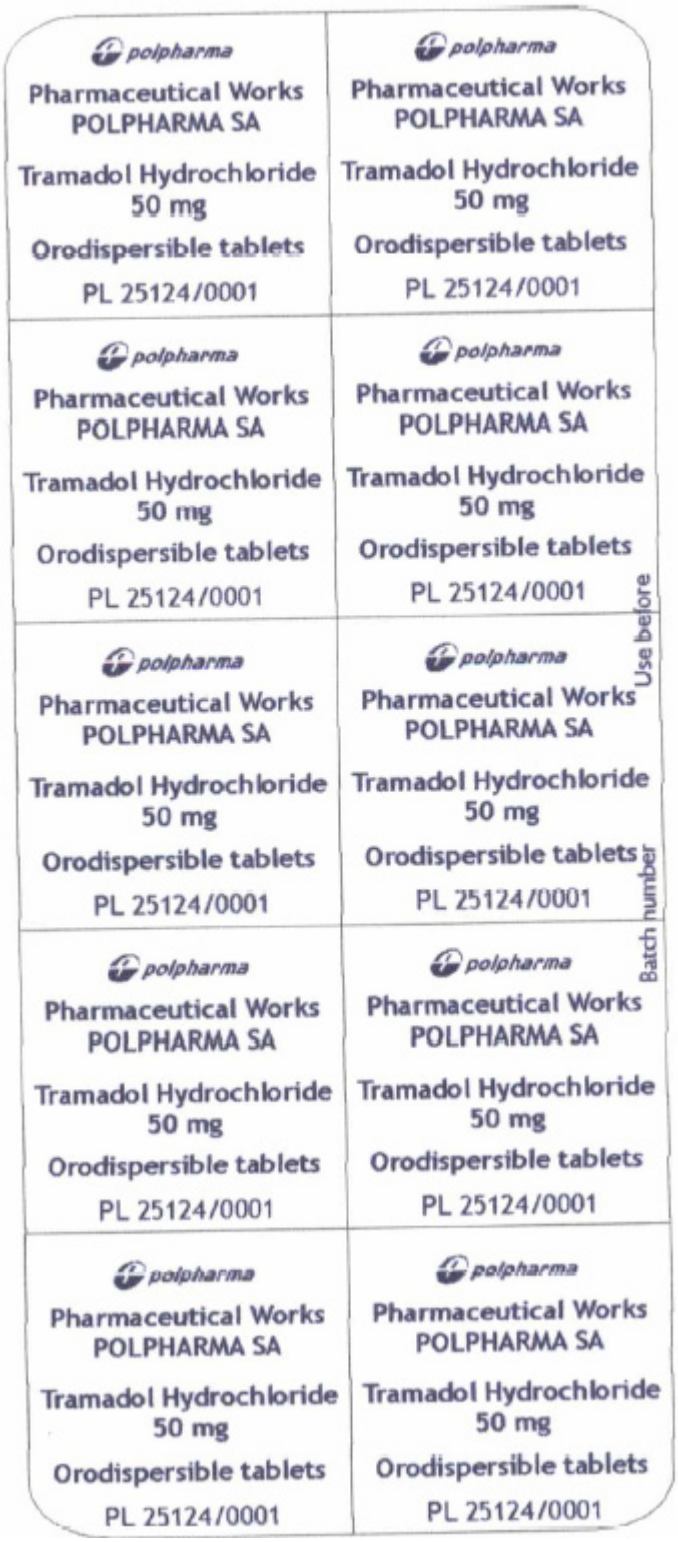
polpharma
Pharmaceutical Works POLPHARMA SA
Tramadol Hydrochloride 50 mg
Orodispersible tablets
PL 25124/0001
Use before
Batch number