Public Assessment Report

Tramadol Hydrochloride 50mg Orodispersible Tablets

Tramadol Hydrochloride

PL 25124/0001

Pharmaceutical Works Polpharma SA

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific Discussion</td>
<td>3</td>
</tr>
<tr>
<td>Overall Conclusion And Risk Benefit/Analysis</td>
<td>8</td>
</tr>
<tr>
<td>Steps Taken During Assessment</td>
<td>9</td>
</tr>
<tr>
<td>Steps Taken After Assessment</td>
<td>10</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>11</td>
</tr>
<tr>
<td>Labels and Leaflet</td>
<td>19</td>
</tr>
</tbody>
</table>
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 (Ethyp Pharm 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.

\[ \text{AUC}_{(0-t)}, \text{ AUC}_{(0-inf)}, \text{C}_{\text{max}}, t_{\text{max}} \text{ and } t_{\frac{1}{2}} \] were calculated according normal standard procedures. Statistical evaluation was performed for \[ \text{AUC}_{(0-t)}, \text{ AUC}_{\text{inf}} \text{ and } \text{C}_{\text{max}} \] 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:

<table>
<thead>
<tr>
<th>Used test for the statistical comparison</th>
<th>Tmax</th>
<th>t₁/₂</th>
<th>Cmax</th>
<th>AUC₀₋ₜ</th>
<th>AUC₀₋∞</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANNOVA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>N.S.</td>
<td>N.S.</td>
<td>S.(p&lt;0.001)</td>
<td>S.(p&lt;0.05)</td>
<td>S.(p&lt;0.05)</td>
</tr>
<tr>
<td>Subject</td>
<td>N.S.</td>
<td>N.S.</td>
<td>S.(p&lt;0.001)</td>
<td>S.(p&lt;0.05)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power of the study</td>
<td></td>
<td>0.983</td>
<td></td>
<td>&gt;0.999</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Bioequivalence test

- 90% standard confidence interval
- Two one-sided T-tests (Schuirmann)
- Geometric mean ratio T/R

<table>
<thead>
<tr>
<th>Tmax</th>
<th>Cmax</th>
<th>AUC₀₋ₜ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANNOVA (Latin square design)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Subject</td>
<td>N.S.</td>
<td>S.(p&lt;0.001)</td>
</tr>
<tr>
<td>Period</td>
<td></td>
<td>N.S.</td>
</tr>
<tr>
<td>Power of the study</td>
<td></td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Bioequivalence test

- Can conclude equivalence

<table>
<thead>
<tr>
<th>Tmax</th>
<th>Cmax</th>
<th>AUC₀₋ₜ</th>
</tr>
</thead>
</table>

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**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the application on 5\textsuperscript{th} May 2006.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 3\textsuperscript{rd} August 2006.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 5\textsuperscript{th} February 2007 and 14\textsuperscript{th} June 2007 and on the medical assessment on 14\textsuperscript{th} December 2006.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 20\textsuperscript{th} April 2007, 10\textsuperscript{th} July 2007 and 18\textsuperscript{th} September 2007 and on the medical assessment on 23\textsuperscript{rd} March 2007.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 18\textsuperscript{th} December 2007.</td>
</tr>
</tbody>
</table>
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 to clinical need.

Pain associated with chronic conditions:
Use an initial dose of 50 mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as
withdrawal symptoms and dependence have been reported (see section 4.4 Special warnings and 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 precautions 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 (t½c) was 6.0 ± 1.5 hours in young volunteers. Tramadol pharmacokinetics show little age dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, t½c was 7.0 ± 1.6 hours on oral administration. Since tramadol is eliminated both metabolically and renally, the terminal half-life t½c may be prolonged in impaired hepatic or renal function. However, the increase in the t½c values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t½c tramadol was a mean of 13.3 ± 4.9 hours; in patients with renal insufficiency (creatinine clearance < 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 (à 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
UKPAR Pharmaceutical Works Polpharma SA, Tramadol Hydrochloride 50mg Orodispersible Tablets  20
After taking very high doses, pin-point pupils, vomiting, fall in blood pressure, fast heart beat, collapse, disturbed consciousness up to coma (deep unconsciousness), epilepsy 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 or for whatever reason, 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, nervous, anxious or shifty. They may be hyperventilated, have difficulty sleeping and experience stomach or bowel disorders. These effects usually disappear after a few days.

If you experience any of these side effects, 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:
- difficulty breathing,
- your urine is getting worse,
- you have an allergic reaction (swelling, itch, rash, itching, narrowing of airways, fainting),
- skin rash, swelling of the face or breathing,
- a fall,
- 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 (seeing things that are not real),
- abuse and withdrawal symptoms (see also section 4. How to take Tramadol tablets - If you stop taking Tramadol tablets),
- false sense of greatness (dysphoria and 'high'),
- 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 these 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: stearic acid, colloidal silicon dioxide, mannitol (E421), crospovidone, sodium starch glycinate, 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 Authorisation Holder:
Pharmaceutical Works Polpharma SA
19 Pełniski Street, 85-200 Stargard Gdanski
POLAND

Manufacturers:
PPA PHARMA INDUSTRIES
2, rue de Saint-Andoix
85170 Chatenay-en-Thymerais
FRANCE

This leaflet was last approved in

UKPAR Pharmaceutical Works Polpharma SA, Tramadol Hydrochloride 50mg Orodispersible Tablets
Tramadol Hydrochloride 50 mg orodispersible tablets

10 tablets

Tramadol Hydrochloride 50 mg orodispersible tablets

Orodispensible tablet containing 50mg of Tramadol Hydrochloride


Braille inscriptions on the front side of the box.
| UKPAR Pharmaceutical Works Polpharma SA, Tramadol Hydrochloride 50mg Orodispersible Tablets | 24 |