

Public Assessment Report

**Trazodone 50mg Tablets
Trazodone 100mg Tablets**

PL 15773/0427

PL 15773/0428

Ratiopharm GmbH

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Lay Summary

Trazodone hydrochloride is an antidepressant indicated for relief of symptoms of all types of depression, including depression accompanied by anxiety. This product was granted a Market Authorisation on 14th February 2006 on the legal basis of essential similarity to the reference product Molipaxin. No new or unexpected safety concerns arose during the assessment of these products and in view of the positive risk/benefit for these products a Market Authorisation was granted.

Scientific Discussion

INTRODUCTION

This Public Assessment Report is based on the assessment report for two standard national abridged licence applications for Trazodone hydrochloride 50mg Capsules (PL 15773/0427) and Trazodone Hydrochloride 100mg Capsules (PL 15773/0428) from Ratiopharm GmbH. The application was made under Article 10.1 essential similarity to Molipaxin 50/100mg Capsules PL 00109/0045 & 0046, first authorised to Roussel Laboratories Ltd, 11 July 1980.

Trazodone hydrochloride is an antidepressant indicated for relief of symptoms of all types of depression, including depression accompanied by anxiety.

PHARMACEUTICAL ASSESSMENT

Active Substance – Trazodone Hydrochloride

The manufacturer of Trazodone hydrochloride is a source of this active to other licensed products. A copy of the open part DMF was submitted, together with a letter of access. An assurance is given that the applicant would be informed of all significant changes in the process or final purification which have an influence on the quality or stability of the product. This active source has been used in granted oral products.

There is a BP monograph for trazodone hydrochloride and the specification proposed by applicant/AIM is consistent with BP requirements. Tests for appearance, solubility, identification and detection of impurities are carried out by both active substance manufacturer and finished product manufacturer and are in compliance with requirements of the European Pharmacopoeia or validation data has been provided for in house methods. Satisfactory accelerated and long-term stability data are provided.

Finished Product

The appearance of the finished product is:

50mg: Green-violet, size 3 capsules filled with white powder.

100mg: yellow-violet, size 2 capsules filled with white powder.

The qualitative formulation for the powder in the capsules are summarised below.

Trazodone HCl

Lactose monohydrate

Colloidal silica anhydrous

Magnesium stearate

Capsules are packaged in PVC/aluminium blisters.

Developmental Pharmaceutics

The objective of the development programme was to formulate a robust, stable, acceptable formulation of trazodone that was essentially similar to the reference product and this aim was achieved.

Manufacturer of Finished Product

A satisfactory manufacturing permit covering GMP has been supplied by the manufacturers. Satisfactory batch data was provided. An acceptable description of the manufacturing process and process controls was provided along with the necessary validation data.

Clinical Trial Formula

A bioequivalence study has been performed comparing the applicant's 100mg capsules vs Molipaxin 100mg capsules. The formulation used in the bioequivalence study is identical to that proposed for marketing. Active from the proposed source has been used to manufacture biobatch. Comparative dissolution profile data of test and reference product have been submitted and dissolution profiles support bioequivalence.

Manufacturing Method, In-Process Controls & Process Validation

A satisfactory GMP compliance certificate issued by an EEA authority covers capsule manufacture and activities proposed was submitted.

A satisfactory manufacturing formula, description of manufacturing process and process controls has been provided. Testing frequency has been stated and is satisfactory. Satisfactory process validation has been carried out and batch data provided.

1.1.1 Excipients

The excipients in the powder blend all comply with their respective current PhEur monographs. Typical Certificates of Analysis from the dosage form manufacturers are provided.

1.1.2 TSE/AHO

Magnesium stearate obtained from FACI and of vegetable origin and is satisfactory. Lactose monohydrate is obtained from DMV. The manufacturer has stated that the lactose is manufactured from cows milk sourced from healthy animals in the same conditions as milk for human consumption and rennet used for the production of whey is in accordance with Public Statement EMEA/CPMP/571/02..

1.1.3 Packaging Materials

Capsules are packaged in transparent PVC 0.250mm/Al 0.025mm foil blisters. The Al foil is lacquered (acrylic resins or nitro-cellulose) on one side for printing and heat sealed lacquered (acrylic resins based on copolymer of vinyl chloride and vinyl acetate modified with maleic anhydride) for PVDC/PVC. The specifications and test methods for the packaging materials have been provided and include identification tests for Al and PVC – IR.

The specifications proposed are in line with Ph.Eur general requirements for hard gelatin capsules. Test methods have been described and are basically standard Ph.Eur procedures. The method for monitoring dissolution has been satisfactorily validated for specificity, linearity, repeatability, intermediate precision, accuracy and stability of reference solution. The two methods for testing of related substances have been satisfactorily validated.

Finished Product Stability.

Stability studies have been provided for and data provided supports the shelf-life of 3 years.

Bioequivalence Studies

Trazodone HCl is well absorbed after oral administration. Absorption is delayed but enhanced by food. The area under the plasma concentration time curve is directly proportional to dosage after oral administration of 25-100mg doses.

A single dose, randomised, two period, crossover study has been carried out comparing the applicant's 100 mg Capsules (BN 135/00, assay 98.2%) with Molipaxin 100 mg capsules (Aventis UK, BN 070655, assay 99.1%). The study was carried out in 40 healthy, non-smoking male and female volunteers (all completed), under fed conditions.

After an overnight fast, volunteers received an oral dose of 1x 100mg capsule of either test or reference product with 240ml water, within 5 minutes of completion of a standardised high fat breakfast. A washout period of 7 days was used between doses. Blood samples for the determination of active levels were taken pre-dose, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 7, 9, 12, 16, 24, 36 and 48 hours post dosing. The half-life of trazodone is 5 to 9 hours, so this time period is suitable. After extraction from plasma, levels of active have been analysed using a validated GC method with doxapram as internal standard (LLOQ 10.8ng/ml).

The results were analysed using ANOVA and confidence intervals were calculated for C_{max} and AUC. The 90% confidence intervals for both parameters are within the 0.8 to 1.25 limit recommended by guidelines. The applicant's 100mg and UK Molipaxin 100mg capsules can be considered bioequivalent.

No bioequivalence studies have been performed to support the bioequivalence of the 50mg capsules. Both strengths are manufactured by the same manufacturer and process, pharmacokinetics is linear over the therapeutic dose range, apart from differences in capsule shell composition the qualitative and quantitative composition of the powder blend are the same. After request for further data on dissolution profiles of the 50mg tablets, bioequivalence was accepted.

PRE-CLINICAL ASSESSEMENT

No new pre-clinical data were submitted for this product which given the nature of the application is acceptable.

CLINICAL ASSESSMENT

Trazodone is an antidepressant with many of the features of a selective serotonin (5-HT) reuptake inhibitor (SSRI) – possibly due to receptor antagonism rather than inhibition of uptake – but which also blocks α_2 receptors. It has no anticholinergic effects but does have some sedative activity. Apart from its established place in the treatment of depression, it has some definite anxiolytic properties, such that it may be useful in the treatment of combined anxiety/depression.

Indications

The proposed indications are,

Relief of symptoms in anxiety and all types of depressive illness including depressive illness accompanied by anxiety.

Dose & Dose Schedule

DEPRESSION AND DEPRESSION ACCOMPANIED BY ANXIETY

Adults:

Initially 150 mg/day in divided doses after food or as a single dose before bedtime. This may be increased up to 300 mg/day in single or divided doses. The major portion of a divided dose to be taken before bedtime. The dose may be further increased to 600 mg/day in divided doses in hospitalised patients.

Elderly patients:

For very elderly or frail patients initially 100 mg/day in divided doses or as a single night-time dose. This may be increased, under supervision, according to efficacy and tolerance. It is unlikely that 300 mg/day will be exceeded.

Children and adolescents below the age of 18 years:

Not recommended, as safety and efficacy have not been established in this population.

ANXIETY

Adults:

75 mg/day increasing to 300 mg/day as necessary.

Toxicology

No formal data is considered to be required for this application.

Clinical Pharmacology

The bioequivalence study is discussed above. Bioequivalence was demonstrated by the results obtained from the statistical analysis of the data is considered sufficient to demonstrate essential similarity or equivalence and allow inter changeability of the test and the reference products to be claimed.

Efficacy

No new data has been supplied and none is considered required for this application.

Safety

No new data has been supplied and none is considered required for this application.

Expert Report

The expert report is satisfactory.

Summary Of Product Characteristics

The proposed Summary of Product Characteristics (SmPCs) for these Trazodone Hydrochloride capsules are considered satisfactory after changes to reflect the prescribing information provided in Sections 4 and 5 of the Summary of Product Characteristics for the *essentially similar* UK cross-reference MOLIPAXIN products, PLs 00109/0045/0046/0133.

Patient Information Leaflet

The proposed Patient Information Leaflets (PILs) for these Trazodone tablet and capsules are considered satisfactory after changes to reflect the prescribing information provided in Sections 4 and 5 of the Summary of Product Characteristics for the *essentially similar* UK cross-reference MOLIPAXIN products PLs 00109/0045/0046/0133.

Labelling

The proposed labelling has been considered by the pharmaceutical assessor.

Discussion

The data presented have shown that the comparative bioavailability study confirmed bioequivalence with the originator product while the safety profile is the same. A Marketing Authorisation was granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

Quality

The quality characteristics of Trazodone are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch and the product was found to be essentially similar to the reference product. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Preclinical

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

Efficacy

No new efficacy data were submitted and none are required for this type of application. Bioequivalence with the reference product was established.

Risk Benefit Assessment

The quality of the product is acceptable and the product is essentially similar to the reference product the product has a positive risk/benefit assessment.

Steps Taken During Assessment

1	The MHRA received the application on 6 th May 2003.
2	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 4 th Dceceberr 2003 and 17 th November 2004. Further information on the clinical assessment was requested on 12 th August 2003.
3	The applicant provided further information in regard to the quality assessment on 4 th December 2003 and 25 th January 2005. Further information in regard of the clinical assessment was received on 28 th November 2003..
4	The application was determined on 14 th February 2006.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trazodone hydrochloride 50 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg trazodone hydrochloride.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Capsules, hard

Hard gelatin green-violet coloured capsules, size 3, printed with T50.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Relief of symptoms of all types of depression including depression accompanied by anxiety.

4.2. Posology and method of administration

Route of administration

Oral

Trazodone hydrochloride Capsules should be taken after food.

DEPRESSION AND DEPRESSION ACCOMPANIED BY ANXIETY

Adults:

Initially 150 mg/day in divided doses after food or as a single dose before bedtime. This may be increased up to 300 mg/day in single or divided doses. The major portion of a divided dose to be taken before bedtime. The dose may be further increased to 600 mg/day in divided doses in hospitalised patients.

Elderly patients:

For very elderly or frail patients initially 100 mg/day in divided doses or as a

single night-time dose. This may be increased, under supervision, according to efficacy and tolerance. It is unlikely that 300 mg/day will be exceeded.

Children and adolescents below the age of 18 years:

Not recommended, as safety and efficacy have not been established in this population.

ANXIETY

Adults:

75 mg/day increasing to 300 mg/day as necessary.

4.3. Contraindications

Known sensitivity to trazodone hydrochloride or to any of the excipients.

4.4. Special warnings and precautions for use

Care should be exercised when administering trazodone hydrochloride to patients suffering from epilepsy, avoiding in particular, abrupt increase or decrease in dosage.

Trazodone hydrochloride should be administered with care in patients with hepatic, renal or cardiac disease.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other medicinal products and other forms of interaction

Although no untoward effects have been reported, trazodone hydrochloride may enhance the effects of muscle relaxants and volatile anaesthetics. Similar considerations apply to combined administration with sedative and antidepressant drugs, including alcohol. Trazodone hydrochloride has been well tolerated in depressed schizophrenic patients receiving standard phenothiazine therapy and also in depressed parkinsonian patients receiving therapy with levodopa.

Possible interactions with Monoamine Oxidase Inhibitors (MAOIs) have occasionally been reported. Although some clinicians do give both concurrently, concurrent administration with MAOIs or within two weeks of stopping MAOIs are not given within one week of stopping trazodone hydrochloride.

Since trazodone hydrochloride is only a very weak inhibitor of noradrenaline re-uptake and does not modify the blood pressure response to tyramine, interference with the hypotensive action of guanethidine-like compounds is unlikely. However, studies in laboratory animals suggest that trazodone hydrochloride may inhibit most of the acute actions of clonidine. In the case of other types of anti-hypertensive drug, although no clinical interactions have been reported, the possibility of potentiation should be considered.

Concurrent use with trazodone may result in elevated serum levels of digoxin and phenytoin. Monitoring of serum levels should be considered in these patients.

4.6. Pregnancy and lactation

Although studies in animals have not shown any direct teratogenic effect, the safety of trazodone hydrochloride in human pregnancy has not been established. On basic principles, therefore, its use during the first trimester should be avoided.

The possibility of trazodone hydrochloride being excreted in the milk should also be considered in nursing mothers.

4.7. Effects on ability to drive and use machines

As with all other drugs acting on the central nervous system, patients should be warned against the risk of handling machinery and driving.

4.8. Undesirable effects

Trazodone hydrochloride is a sedative antidepressant and drowsiness, sometimes experienced during the first days of treatment, usually disappears on continued therapy.

Anticholinergic-like symptoms do occur but the incidence is similar to placebo.

The following symptoms, most of which are commonly reported in cases of untreated depression, have also been recorded in small numbers of patients receiving trazodone hydrochloride therapy: dizziness, headache, nausea and vomiting, weakness, decreased alertness, weight loss, tremor, dry mouth,

bradycardia, tachycardia, postural hypotension, oedema, constipation, diarrhoea, blurred vision, restlessness, confusional states, insomnia and skin rash.

Blood dyscrasias, including agranulocytosis, thrombocytopenia and anaemia, have been reported on rare occasions. Adverse effects on hepatic function, including jaundice and hepatocellular damage, sometimes severe, have been rarely reported. Should such effects occur, trazodone hydrochloride should be discontinued immediately.

As with other drugs with alpha-adrenolytic activity, trazodone hydrochloride has very rarely been associated with priapism. This may be treated with an intracavernosum injection of an alpha-adrenergic agent such as adrenaline or metaraminol. However there are reports of trazodone-induced priapism which have required surgical intervention or led to permanent sexual dysfunction. Patients developing this suspected adverse reaction should cease trazodone hydrochloride immediately.

In contrast to the tricyclic antidepressants, trazodone hydrochloride is devoid of anticholinergic activity. Consequently, troublesome side effects such as dry mouth, blurred vision and urinary hesitancy have occurred no more frequently than in patients receiving placebo therapy. This may be of importance when treating depressed patients who are at risk from conditions such as glaucoma, urinary retention and prostatic hypertrophy.

Studies in animals have shown that trazodone hydrochloride is less cardiotoxic than the tricyclic antidepressants, and clinical studies suggest that the drug may be less likely to cause cardiac arrhythmias in man. Clinical studies in patients with pre-existing cardiac disease indicate that trazodone may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated premature ventricular contractions, ventricular couplets, and short episodes (3-4 beats) of ventricular tachycardia.

Trazodone hydrochloride has had no effect on arterial blood pCO₂ or pO₂ levels in patients with severe respiratory insufficiency due to chronic bronchial or pulmonary disease.

4.9. Overdose

The most frequently reported reactions to overdose have included drowsiness, dizziness and vomiting. There is no specific antidote to *Trazodone hydrochloride Capsules*. The stomach should be emptied as quickly as possible followed by the oral administration of activated charcoal. Treatment should be symptomatic and supportive in the case of hypotension and excessive sedation.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

2 PHARMACOTHERAPEUTIC GROUP

Antidepressant.

ATC code: N06AX05

Trazodone hydrochloride is a potent antidepressant. It has also anxiety reducing activity. Trazodone hydrochloride is a triazolopyridine derivative chemically unrelated to known tricyclic, tetracyclic and other antidepressant agents. It has negligible effect on noradrenaline re-uptake mechanisms. Whilst the mode of action of trazodone hydrochloride is not known precisely, its antidepressant activity may concern noradrenergic potentiation by mechanisms other than uptake blockade. A central antiserotonin effect may account for the drug's anxiety reducing properties.

5.2. Pharmacokinetic properties

Trazodone is rapidly absorbed from the gastro-intestinal tract and extensively metabolised. Paths of metabolism of trazodone include n-oxidation and hydroxylation. The metabolic m-chlorophenylpiperazine is active. Trazodone is excreted in the urine almost entirely in the form of its metabolites, either in free or in conjugated form. The elimination of trazodone is biphasic, with a terminal elimination half-life of 5 to 13 hours. Trazodone is excreted in breast milk.

There was an approximate two-fold increase in terminal phase half-life and significantly higher plasma concentrations of trazodone in 10 subjects aged 65 to 74 years compared with 12 subjects aged 23 to 30 years following a 100 mg dose of trazodone. It was suggested that there is an age-related reduction in the hepatic metabolism of trazodone.

5.3. Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core:

Lactose monohydrate
Colloidal silica, anhydrous
Magnesium stearate

Capsule shell:

Gelatin
Indigo carmine (E132)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Erythrosine (E127)
Patent Blue V (E131)

Printing ink:

Shellac
Titanium dioxide (E171)
Brilliant Blue FCF (E133)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Keep blisters in the outer carton.

6.5. Nature and contents of container

PVC foil of 250 µm thickness and aluminium foil of 25 µm thickness blisters are available in pack sizes of 28, 56, and 84 tablets. Each blister strip contains 14 capsules.

(Not all pack sizes may be marketed)

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Strasse 3
D-89079 Ulm
Germany

8. MARKETING AUTHORISATION NUMBER

PL 15773/0427

**3 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

14/02/2006

4 10 DATE OF REVISION OF THE TEXT

14/02/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trazodone hydrochloride 100 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg trazodone hydrochloride.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Capsules, hard

Hard gelatin yellow-violet coloured capsules, size 2, printed with T100.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Relief of symptoms of all types of depression including depression accompanied by anxiety.

4.2. Posology and method of administration

Route of administration

Oral

Trazodone hydrochloride Capsules should be taken after food.

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ANXIETY

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Trazodone hydrochloride should be administered with care in patients with hepatic, renal or cardiac disease.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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The possibility of trazodone hydrochloride being excreted in the milk should also be considered in nursing mothers.

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5.2. Pharmacokinetic properties

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5.3. Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core:

Lactose monohydrate
Colloidal silica, anhydrous
Magnesium stearate

Capsule shell:

Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)
Erythrosine (E127)
Patent Blue V (E131)

Printing ink:

Shellac
Titanium dioxide (E171)
Brilliant Blue FCF (E133)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Keep blisters in the outer carton.

6.5. Nature and contents of container

PVC foil of 250 µm thickness and aluminium foil of 25 µm thickness blisters are available in pack sizes of 28, 56, and 84 tablets. Each blister strip contains 14 capsules.

(Not all pack sizes may be marketed)

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Strasse 3
D-89079 Ulm
Germany

8. MARKETING AUTHORISATION NUMBER

PL 15773/0428

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AUTHORISATION**

14/02/2006

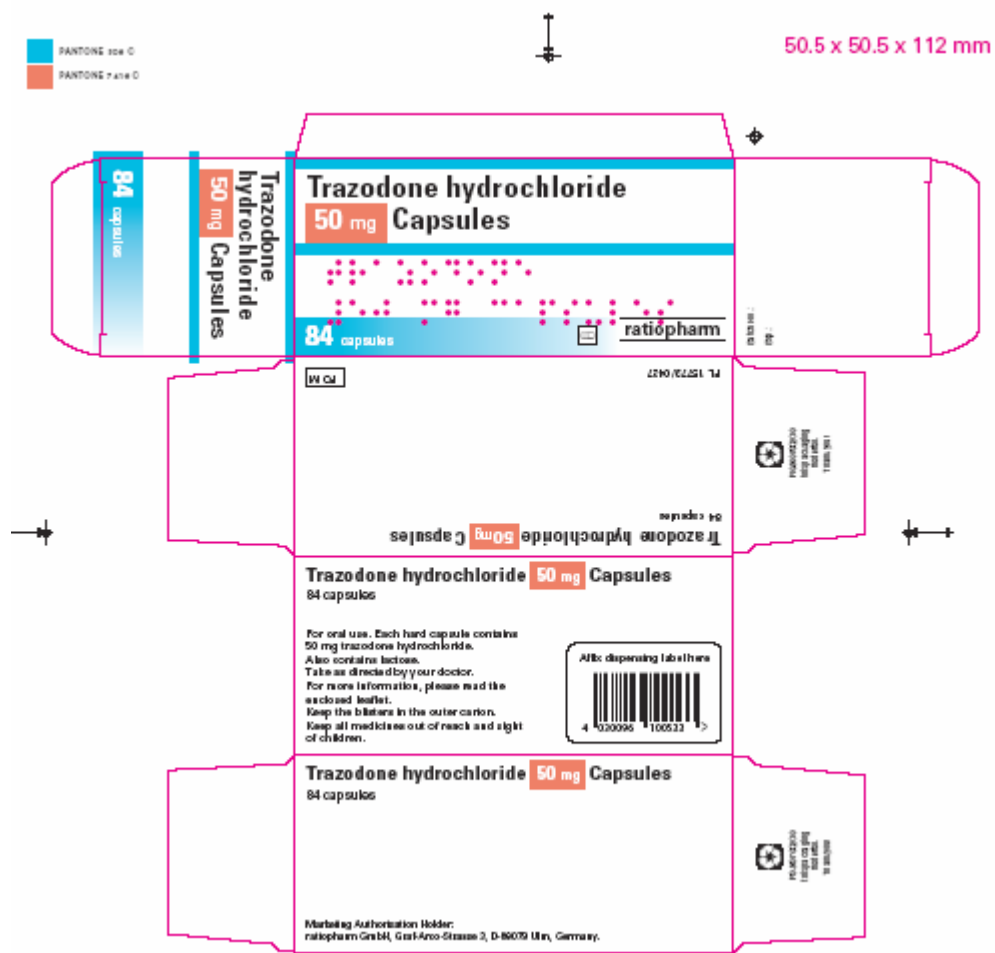
7 10DATE OF REVISION OF THE TEXT

14/02/2006

LABELS AND LEAFLET

Trazodone hydrochloride 50 mg Capsules	Trazodone hydrochloride 50 mg Capsules	Trazodone hydrochloride 50 mg Capsules
ratiopharm GmbH		
<i>Batch No.: and Exp.: see impress</i>		
Trazodone hydrochloride 50 mg Capsules		
Trazodone hydrochloride 50 mg Capsules	Trazodone hydrochloride 50 mg Capsules	Trazodone hydrochloride 50 mg Capsules
ratiopharm GmbH		
<i>Batch No.: and Exp.: see impress</i>		
Trazodone hydrochloride 50 mg Capsules		
Trazodone hydrochloride 50 mg Capsules	Trazodone hydrochloride 50 mg Capsules	Trazodone hydrochloride 50 mg Capsules
ratiopharm GmbH		
<i>Batch No.: and Exp.: see impress</i>		
Trazodone hydrochloride 50 mg Capsules		
Trazodone hydrochloride 50 mg Capsules	Trazodone hydrochloride 50 mg Capsules	Trazodone hydrochloride 50 mg Capsules
Batch No.:		Exp:

↑
Batch and expiry will be overprinted



Patient Information Leaflet

Read this entire leaflet carefully before you start taking this medicine.

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

In this leaflet:

1. What is in *Trazodone hydrochloride Capsules*?
2. What is your medicine used for?
3. Before you take *Trazodone hydrochloride Capsules*
4. How to take *Trazodone hydrochloride Capsules*
5. Possible side effects
6. Storing your *Trazodone hydrochloride Capsules*

ratiopharm

Trazodone hydrochloride 50 mg Capsules

Trazodone hydrochloride 100 mg Capsules

1. What is in *Trazodone hydrochloride Capsules*?

Your doctor has prescribed *Trazodone hydrochloride Capsules*. Your medicine is available in two strengths:

- ***Trazodone hydrochloride 50 mg Capsules***: Each hard capsule contains 50 mg trazodone hydrochloride as active ingredient. The capsules are green-violet coloured and are printed with 'T50'. Your medicine is available in blister packs containing 84 capsules.
- ***Trazodone hydrochloride 100 mg Capsules***: Each capsule contains 100 mg trazodone hydrochloride as active ingredient. The capsules are yellow-violet coloured and are printed with 'T100'. Your medicine is available in blister packs containing 56 capsules.

Both strengths contain the following inactive ingredients: lactose monohydrate, colloidal anhydrous silica, magnesium stearate, gelatin, titanium dioxide (E171), yellow iron oxide (E172), erythrosin (E127) and patent blue V (E131). The 50 mg capsules also contain indigo carmine (E132). The printing ink also contains the following ingredients: shellac, titanium dioxide (E171) and brilliant blue (E133).

Marketing Authorisation Holder:

ratiopharm GmbH, Graf-Arco-Strasse 3, D-89079 Ulm, Germany.

Manufacturer:

Merckle GmbH, Ludwig-Merckle-Strasse 3, D-89143 Blaubeuren, Germany.

2. What is your medicine used for?

Trazodone hydrochloride belongs to a group of medicines called anti-depressants.

Trazodone hydrochloride Capsules are used for the relief of symptoms of all types of depression including depression accompanied by anxiety.

3. Before you take *Trazodone hydrochloride Capsules*

Do not take this medicine if:

- You are allergic to trazodone hydrochloride or to any of the ingredients listed above.

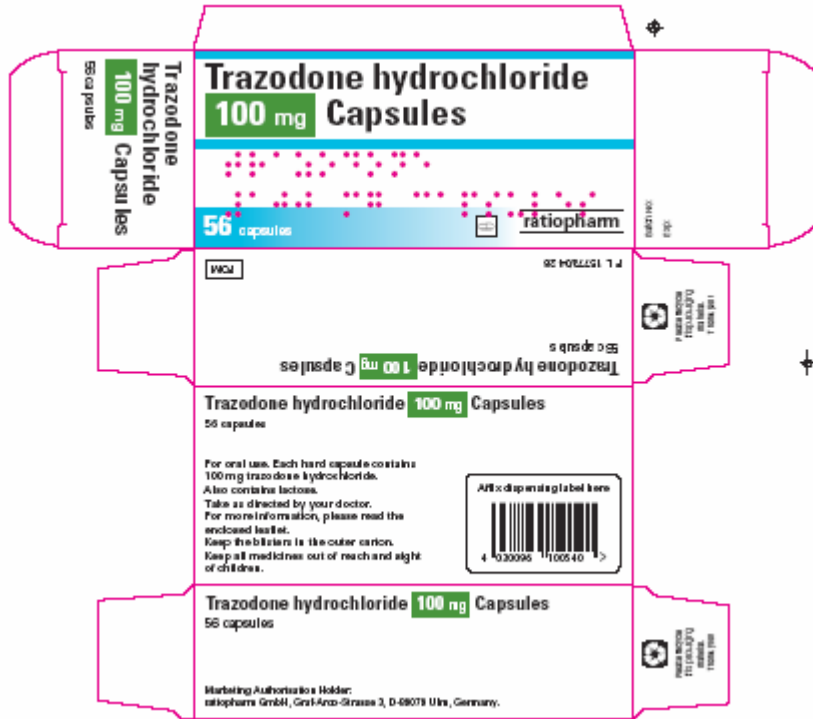
Please tell your doctor before taking this medicine if:

- You are pregnant, think you might be pregnant or are planning to become pregnant.
- You are breast-feeding.
- You suffer from epilepsy.
- You suffer from kidney or liver disease.
- You suffer from heart problems.

Please tell your doctor if you are taking any of the following medicines:

- Muscle relaxants and inhaled anaesthetics. If you go to hospital to have surgery, please inform the anaesthetist that you are taking *Trazodone hydrochloride Capsules*.
- Medicines known as Monoamine Oxidase Inhibitors (MAOIs). **If you have been taking a MAOI, you should not start taking *Trazodone hydrochloride Capsules* for two weeks after stopping the MAOI. A MAOI should not be taken for at least seven days after you have stopped treatment with *Trazodone hydrochloride Capsules*.**
- You are taking clonidine (a medicine used to lower high blood pressure or to treat migraine).
- Medicines used in the treatment of epilepsy (e.g. phenytoin).
- Medicine used in heart disease (e.g. digoxin).





Trazodone hydrochloride 100 mg Capsules	Trazodone hydrochloride 100 mg Capsules	Trazodone hydrochloride 100 mg Capsules
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Batch No.: Exp:		

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Patient Information Leaflet

Read this entire leaflet carefully before you start taking this medicine.

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

In this leaflet:

1. What is in *Trazodone hydrochloride Capsules*?
2. What is your medicine used for?
3. Before you take *Trazodone hydrochloride Capsules*
4. How to take *Trazodone hydrochloride Capsules*
5. Possible side effects
6. Storing your *Trazodone hydrochloride Capsules*

ratiopharm

Trazodone hydrochloride 50 mg Capsules

Trazodone hydrochloride 100 mg Capsules

1. What is in *Trazodone hydrochloride Capsules*?

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- ***Trazodone hydrochloride 50 mg Capsules***: Each hard capsule contains 50 mg trazodone hydrochloride as active ingredient. The capsules are green-violet coloured and are printed with 'T50'. Your medicine is available in blister packs containing 84 capsules.
- ***Trazodone hydrochloride 100 mg Capsules***: Each capsule contains 100 mg trazodone hydrochloride as active ingredient. The capsules are yellow-violet coloured and are printed with 'T100'. Your medicine is available in blister packs containing 56 capsules.

Both strengths contain the following inactive ingredients: lactose monohydrate, colloidal anhydrous silica, magnesium stearate, gelatin, titanium dioxide (E171), yellow iron oxide (E172), erythrosin (E127) and patent blue V (E131). The 50 mg capsules also contain indigo carmine (E132). The printing ink also contains the following ingredients: shellac, titanium dioxide (E171) and brilliant blue (E133).

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2. What is your medicine used for?

Trazodone hydrochloride belongs to a group of medicines called anti-depressants.

Trazodone hydrochloride Capsules are used for the relief of symptoms of all types of depression including depression accompanied by anxiety.

3. Before you take *Trazodone hydrochloride Capsules*

Do not take this medicine if:

- You are allergic to trazodone hydrochloride or to any of the ingredients listed above.

Please tell your doctor before taking this medicine if:

- You are pregnant, think you might be pregnant or are planning to become pregnant.
- You are breast-feeding.
- You suffer from epilepsy.
- You suffer from kidney or liver disease.
- You suffer from heart problems.

Please tell your doctor if you are taking any of the following medicines:

- Muscle relaxants and inhaled anaesthetics. If you go to hospital to have surgery, please inform the anaesthetist that you are taking *Trazodone hydrochloride Capsules*.
- Medicines known as Monoamine Oxidase Inhibitors (MAOIs). **If you have been taking a MAOI, you should not start taking *Trazodone hydrochloride Capsules* for two weeks after stopping the MAOI. A MAOI should not be taken for at least seven days after you have stopped treatment with *Trazodone hydrochloride Capsules*.**
- You are taking clonidine (a medicine used to lower high blood pressure or to treat migraine).
- Medicines used in the treatment of epilepsy (e.g. phenytoin).
- Medicine used in heart disease (e.g. digoxin).



Before taking *Trazodone hydrochloride Capsules* you should tell your doctor of all medicines you are taking, including any that you have bought without a prescription (e.g. from the supermarket).

This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Driving and using machines

Trazodone hydrochloride Capsules can make you drowsy. If affected, you should not drive or operate machinery.

You are advised NOT to drink alcohol when you are being treated with *Trazodone hydrochloride Capsules*.

■ 4. How to take *Trazodone hydrochloride Capsules*

■ The label on the carton will tell you how many capsules you should take and when. Follow your doctor's advice. The capsules should be swallowed whole with water. Your doctor may want you to take your capsules in divided doses after food or as a single dose as you go to bed. If you are not sure how to take your capsules or how many capsules you should take, please speak to your doctor or pharmacist.

Depression and depression accompanied by anxiety: the usual starting dose for adults is 150 mg a day. Your doctor may afterwards decide to increase your daily dose to 300 mg. Elderly or weak people will be prescribed a lower dose of 100 mg a day.

Anxiety: the daily dose may vary from 75 mg to 300 mg a day.

Trazodone hydrochloride Capsules are not recommended for children and adolescents under the age of 18 years.

It is important to continue taking the capsules for as long as your doctor tells you to. You should not suddenly stop taking your capsules without advice from your doctor. When your doctor wants you to stop taking *Trazodone hydrochloride Capsules* the dose will be reduced gradually. Do not change the dose of *Trazodone hydrochloride Capsules* unless you have spoken with your doctor.

What if you miss a dose?

If you forget to take a dose at the right time, take it as soon as you remember. Then go on as before. **Do not take two doses at the same time.**

What if you have taken too many capsules?

If you have accidentally taken too many capsules, contact your nearest casualty department or tell your doctor/pharmacist **immediately**.

5. Possible side effects

As with all medicines, *Trazodone hydrochloride Capsules* can cause some side effects.

In most people, the most common side effect is drowsiness. This occurs during the first few days of your treatment and usually disappears as your treatment continues.

Other common effects reported include: headache, dizziness, nausea (feeling sick), vomiting (being sick), weakness, decreased alertness, tremor, dry mouth, slow or racing heartbeat, skin rash, low blood pressure, swelling of the ankles (oedema), diarrhoea, constipation, blurred vision, restlessness, weight loss, and insomnia (difficulty in sleeping).

Some men have experienced long-lasting and painful erections while taking *Trazodone hydrochloride Capsules*. If this happens to you, stop taking the capsules and talk to your doctor immediately.

Rarely, the following side effects have been reported: jaundice (yellowing of the skin and/or eyes) or other abnormalities of liver function, anaemia, a low white cell count (the blood cells that fight infection) and low platelet count (the blood cells which help the blood clot).

If you suffer from any of these unwanted side effects or any other effects not mentioned in this leaflet, please talk to your doctor.

6. Storing your *Trazodone hydrochloride Capsules*

Keep the blisters in the outer carton.

The expiry date of this product is printed on the carton and blister foil. Do not use *Trazodone hydrochloride Capsules* after this date.

If your doctor tells you to stop taking *Trazodone hydrochloride Capsules*, please take them back to the pharmacist for safe disposal.

Keep *Trazodone hydrochloride Capsules* out of the reach and sight of children
