Public Assessment Report

Decentralised Procedure

Trazodone Hydrochloride 50mg/5ml Oral Solution

(trazodone hydrochloride)

UK licence numbers: PL 20046/0073

Focus Pharmaceuticals Limited
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Focus Pharmaceuticals Limited, a Marketing Authorisation (licence) for the medicinal product Trazodone Hydrochloride 50mg/5ml Oral Solution (PL 20046/0073) on 23rd March 2011. This is a prescription-only medicine (POM).

Trazodone Hydrochloride Oral Solution is used to treat depression, including depression accompanied by feelings of anxiety.

Trazodone hydrochloride belongs to a group of medicines called antidepressants. Everyone has natural substances called serotonin and noradrenaline in their brain which help to lighten their mood. People who are depressed or anxious have lower levels of serotonin and noradrenaline than others. Trazodone works by helping to prolong the mood lightening effect of serotonin and noradrenaline which has been released in the brain.

The proposed product was considered to be a generic version of the UK reference product Molipaxin™ Liquid 50mg/5ml (PL 17780/0542, Winthrop Pharmaceuticals UK Limited) based on the data submitted by Focus Pharmaceuticals Limited.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of Trazodone Hydrochloride 50mg/5ml Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.
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# Module 1

## Information about Initial Procedure

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<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<td>Unit 5, Faraday Court</td>
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Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Trazodone Hydrochloride 50mg/5ml Oral Solution (PL 20046/0073) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Trazodone Hydrochloride 50mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 50mg of Trazodone hydrochloride.

Excipients: sorbitol 350mg/5ml and sodium 3mg/5ml.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution.

Colourless to yellowish clear solution with an orange odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Symptoms of depression likely to respond in the first week of treatment include depressed mood, insomnia, anxiety, somatic symptoms and hypochondriasis.

4.2 Posology and method of administration

Route of administration: Oral.

Adults:

Starting dose is 150mg/day in divided doses after food or as a single dose before retiring. This may be increased to 300mg/day, the major portion of which is preferably taken on retiring. In hospitalised patients dosage may be further increased to 600mg/day.

Children:

There are insufficient data to recommend the use of trazodone in children.

Elderly or Frail:

For elderly or very frail patients initial starting dose 100mg/day in divided doses or as a single night-time dose. This may be increased, under supervision, according to efficacy and tolerance. Doses above 300mg/day are unlikely to be required.

Tolerability may be improved by taking trazodone after food.

In conformity with current psychiatric opinion, it is suggested that trazodone be continued for several months after remission. Cessation of trazodone treatment should be gradual.

4.3 Contraindications

Known sensitivity to trazodone or to any of the excipients.
4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which trazodone is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if those symptoms present.

Trazodone should be administered with care in patients with severe hepatic, renal or cardiac disease. Care should be exercised when administering trazodone to patients suffering epilepsy, avoiding in particular, abrupt increases or decreases in dosage.

Potent CYP3A4 inhibitors may lead to increases in trazodone serum levels. See section 4.5 for further information.

This medicinal product contains 0.13mmol (or 3mg) sodium per 5ml. To be taken into consideration by patients on a controlled sodium diet. It also contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with potent CYP3A4 inhibitors such as erythromycin, ketoconazole, itraconazole, ritonavir, indinavir, and nefazodone. It is likely that potent CYP3A4 inhibitors may lead to substantial increases in trazodone plasma concentrations with the potential for adverse effects. Exposure to ritonavir during initiation or resumption of treatment in patients receiving trazodone will increase the potential for excessive sedation, cardiovascular, and gastrointestinal effects. If trazodone is used with a potent CYP3A4 inhibitor, a lower dose of trazodone should be considered. However, the co-administration of trazodone and potent CYP3A4 inhibitors should be avoided where possible.

Carbamazepine reduced plasma concentrations of trazodone when coadministered. Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taken with carbamazepine.

Although no untoward effects have been reported, trazodone may enhance the effects of muscle relaxants and volatile anaesthetics. Similar considerations apply to combined administration with sedative and anti-depressant drugs, including alcohol.

Trazodone 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 have occasionally been reported. Although some clinicians do give both concurrently, co-administration cannot be recommended nor can the administration of trazodone within two weeks of stopping MAOIs or administration of MAOIs within one week of stopping trazodone.
Since trazodone 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 may inhibit most of the acute actions of clonidine. In the case of other types of antihypertensive 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 or phenytoin. Monitoring of serum levels should be considered in these patients.

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

4.6 Pregnancy and lactation

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

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

Trazodone should only be administered during pregnancy and lactation if considered essential by the physician.

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

Cases of suicidal ideation and suicidal behaviours have been reported during trazodone therapy or early after treatment discontinuation (see section 4.4).

Trazodone 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 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 hepato cellular damage, sometimes severe, have been rarely reported. Should such effects occur, trazodone should be discontinued immediately.

As with other drugs with alpha-adrenergic activity, trazodone 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 immediately.

In contrast to the tricyclic antidepressants, trazodone 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 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.
There have been occasional reports of serotonin syndrome and convulsions associated with the use of trazodone, especially when associated with other psychotropic drugs. Neuroleptic malignant syndrome may, very rarely, arise in the course of treatment with trazodone.

Hyponatraemia has been reported in association with treatment with trazodone. Fluid and electrolyte status should be monitored in symptomatic patients.

Trazodone 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

Features of Toxicity

The most frequently reported reactions to overdose have included drowsiness, dizziness, nausea and vomiting. In more serious cases coma, tachycardia, hyponatremia, convulsions and respiratory failure have been reported. Cardiac features may include bradycardia, QT prolongation and torsade de pointes. Symptoms may appear 24 hours or more after overdose.

Overdoses of trazodone in combination with other antidepressants may cause serotonin syndrome.

Management

There is no specific antidote to trazodone. Activated charcoal should be considered in adults who have ingested more than 1g trazodone, or in children who have ingested more than 150mg trazodone within 1 hour of presentation. Alternatively, in adults, gastric lavage may be considered within 1 hour of ingestion of a potentially life-threatening overdose.

Observe for at least 6 hours after ingestion (or 12 hours if a sustained release preparation has been taken). Monitor BP, pulse and GCS. Monitor oxygen saturation if GCS is reduced. Cardiac monitoring is appropriate in symptomatic patients.

Single brief convulsions do not require treatment. Control frequent or prolonged convulsions with intravenous diazepam (0.1-0.3mg/kg body weight) or lorazepam (4mg in an adult and 0.05mg/kg in a child). If these measures do not control the fits, an intravenous infusion of phenytoin may be useful. Give oxygen and correct acid base and metabolic disturbances as required.

Treatment should be symptomatic and supportive in the case of hypotension and excessive sedation. If severe hypotension persists consider use of inotropes, eg dopamine or dobutamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N06A X05. Other antidepressants.

Trazodone is a triazolopyridine derivative which differs chemically from other currently available antidepressants. Although trazodone bears some resemblance to the benzodiazepines, phenothiazines and tricyclic antidepressants, its pharmacological profile differs from each of these classes of drugs. The basic idea for the development of trazodone was the hypothesis that depression involves an imbalance of the mechanism responsible for the emotional integration of unpleasant experiences. Consequently, new animal models of depression consisting of responses to unpleasant or noxious stimuli, instead of the current tests related to the aminergic theory of depression, were used in studying the drug. Trazodone inhibits serotonin uptake into rat brain synaptosomes and by rat platelets at relatively high concentrations and inhibits brain uptake of noradrenaline \textit{in vitro} only at very high concentrations. It possesses antiserotonin-adrenergic blocking and analgesic effects. The anticholinergic activity of trazodone is less than that of the tricyclic antidepressants in animal studies and this has been confirmed in therapeutic trials in depressed patients.

The electroencephalographic profile of trazodone in humans is distinct from that of the tricyclic antidepressants or the benzodiazepines, although bearing some resemblance to these agents in its effect in certain wavebands. Studies of the cardiovascular effects of trazodone in humans, His bundle and surface electrocardiograms in dogs, and experience with overdosage in man indicate that trazodone is less liable than imipramine to cause important adverse effects on the heart. However, studies in depressed patients with significant cardiac impairment suggest that trazodone may aggravate existing ventricular arrhythmias in a small undefined subgroup of such patients.
5.2 Pharmacokinetic properties

Peak plasma concentrations are attained about 1.5 hours after oral administration of trazodone. Absorption is delayed and somewhat enhanced by food. The area under the plasma concentration-time curve is directly proportional to dosage after oral administration of 25 to 100mg. Trazodone is extensively metabolised, less than 1% of an oral dose being excreted unchanged in the urine. The main route of elimination is via the kidneys with 70 to 75% of an oral dose being recovered in the urine within the first 72 hours of ingestion. The elimination half-life for unchanged drug has been reported to be about 7 hours.

In vitro studies in human liver microsomes show that trazodone is metabolised by cytochrome P4503A4 (CYP3A4) to form m-chlorophenylpiperazine. Whilst significant, the role of this pathway in the total clearance of trazodone in vivo has not been fully determined.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic acid
Saccharin sodium
Hypermellose
Sorbitol, liquid (non-crystallising)
Glycerol
Orange flavour
Citric acid monohydrate
Sodium citrate
Water, purified.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months unopened.
Once the bottle is open, use within 1 month.

6.4 Special precautions for storage

Do not store above 25°C.
Keep bottle in the outer carton to protect from light.

6.5 Nature and contents of container

Amber type III glass bottle, sealed with a high density polyethylene (HDPE) tamper evident closure, containing 120ml of solution.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Limited
Unit 5, Faraday Court
First Avenue
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Burton upon Trent
Staffordshire
DE14 2WX
8 MARKETING AUTHORISATION NUMBER(S)
PL 20046/0073

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/03/2011

10 DATE OF REVISION OF THE TEXT
23/03/2011
Module 3

Product Information Leaflet

Trazodone Hydrochloride 50mg/5ml Oral Solution

Seven important things you need to know about Trazodone Oral Solution.

- **Trazodone Oral Solution treats depression and depression accompanied by anxiety.** Like all medicines it can cause side effects. Before you start taking your medicine it is important that you and your doctor discuss the benefits of treatment against the possible side effects (see section 4, Possible side effects).

- **Trazodone Oral Solution should not be used by children** (see section 3, How to take Trazodone Oral Solution).

- **Some people who are depressed or anxious think of harming or killing themselves.** If you start to feel worse, or think of harming or killing yourself, see your doctor or go to a hospital straight away (see section 4, Possible side effects).

- **Trazodone Oral Solution may not work straight away.** Some people taking antidepressants feel worse before feeling better. Your doctor should ask to see you again in a couple of weeks after you first start treatment. Tell your doctor if you haven’t started feeling better (see section 3, How to take Trazodone Oral Solution).

- **Don’t stop taking Trazodone Oral Solution without talking to your doctor** (see section 3, How to take Trazodone Oral Solution).

- **Taking some other medicines with Trazodone Oral Solution can cause problems.** You may need to talk to your doctor (see section 2, Before you take Trazodone Oral Solution).

- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Read all of this leaflet. It includes a lot of important information about this medicine.

This medicine has been prescribed for you. Do not pass it onto others. It may harm them, even if their symptoms are the same as yours.

Keep this leaflet. You may need to read it again.
If you have any further questions, ask your doctor or pharmacist.
You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

In this leaflet:
1. What Trazodone Oral Solution is and what it is used for
2. Before you take Trazodone Oral Solution
3. How to take Trazodone Oral Solution
4. Possible side effects
5. How to store Trazodone Oral Solution
6. Further information

1. What Trazodone Oral Solution is and what it is used for

Your medicine is called Trazodone Hydrochloride 50mg/5ml Oral Solution (called Trazodone Oral Solution throughout the rest of this leaflet).

What this medicine does

Your doctor has prescribed Trazodone Oral Solution to treat depression, including depression accompanied by feelings of anxiety.

Trazodone hydrochloride belongs to a group of medicines called antidepressants. Everyone has natural substances called serotonin and noradrenaline in their brain which help to lighten your mood. People who are depressed or anxious have lower levels of serotonin and noradrenaline than others. Trazodone works by helping to prolong the mood lightening effect of serotonin and noradrenaline which has been released in the brain.

2. Before you take Trazodone Oral Solution

Do not take Trazodone Oral Solution:

- if you are allergic (hypersensitive) to trazodone or any of the other ingredients of Trazodone Oral Solution (see section 6, Further information).

Symptoms of an allergic reaction may include a red and lumpy skin rash, difficulty breathing, swelling of eyelids, face, lips, mouth or tongue, unexplained high temperature (fever) and feeling faint. If the swelling affects your throat and makes breathing and swallowing difficult, go to hospital straight away.

Discuss with your doctor or pharmacist if any of the following apply to you:

- if you have problems with your liver, kidneys or heart;
- if you have epilepsy (fits). Your doctor will monitor your dosage carefully;
• if you are going to have an operation where you will need a general anaesthetic;
• if you are taking antibiotics e.g. erythromycin;
• if you are taking medicines used to treat fungal infections e.g. ketoconazole, itraconazole;
• if you are taking medicines used to treat HIV e.g. ritonavir and indinavir.

Taking these medicines with trazodone hydrochloride could increase the side effects (see section below, Using other medicines with Trazodone Oral Solution).

Take special care when using Trazodone Oral Solution
• if you are having a surgical operation or dental procedure, where you will be put to sleep, tell your doctor you are taking Trazodone Oral Solution as it may affect drugs you are given during the procedure.

Using other medicines with Trazodone Oral Solution
Make sure that your doctor knows if you are taking another medicine listed here:
• **Erythromycin** (an antibiotic, used to treat infections); If taken with trazodone, you may have more serious side effects and your doctor may decide to change your dose of Trazodone Oral Solution.
• **Ketoconazole** or **itraconazole** (used to treat fungal infections); If taken with trazodone, you may have more serious side effects and your doctor may decide to change your dose of Trazodone Oral Solution.
• **Ritonavir or Indinavir** (for HIV infections); if taken with trazodone your doctor may need to change your dose of Trazodone Oral Solution and you may experience increased side effects.
• **Carbamazepine** (used to control epilepsy and also to treat serious mood disorders e.g. manic depression); If taken with trazodone your doctor will need to monitor you carefully and may need to change your dose of Trazodone Oral Solution.
• **Muscle relaxants** such as diazepam (used to relieve muscle spasms); if taken with trazodone your doctor may need to change your dose of muscle relaxant.
• **Inhaled anaesthetics** (used to put you to sleep prior to an operation), or other **muscle relaxants** (used to relax the muscles prior to surgical procedures); if you are planning to have an operation, tell the anaesthetist, or dentist, that you are taking Trazodone Oral Solution.
• **Other sedative and antidepressant drugs** e.g. diazepam (a sedative, used to help you relax) and citalopram (used for treating depression); If taken with trazodone your doctor may need to change the dose of your medicines.
• **Monoamine Oxidase Inhibitors (MAOIs)** such as phenelzine,
isocarboxazid, tranylcypromine and moclobemide, used to treat depression and selegiline, used to treat Parkinson’s disease.

- **Wait 14 days** after stopping an MAOI before you take Trazodone Oral Solution.
- **Wait 7 days** after stopping Trazodone Oral Solution before starting an MAOI.

- **Clonidine** (used to treat high blood pressure, migraine and menopausal flushing): if taken with trazodone this medicine may not be as effective.

- **Other drugs used to treat high blood pressure** e.g. captopril, valsartan: if taken with trazodone these medicines may not be as effective.

- **Digoxin** (used to treat heart failure and other heart problems): if taken with trazodone your doctor will need to monitor you carefully.

- **Phenytoin** (used to control epilepsy): if taken with trazodone your doctor will need to monitor you carefully.

Tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines; including ones you have bought yourself.

### Taking Trazodone Oral Solution with food and alcohol

- Trazodone Oral Solution can be taken with, or without food (see section 3, How to take Trazodone Oral Solution). Taking Trazodone Oral Solution with food can help to lower the chances of side effects such as feeling or being sick.

- **Talk to your doctor about drinking alcohol whilst taking Trazodone Oral Solution.**

### Pregnancy and breast-feeding

If you are pregnant, thinking of becoming pregnant, or breast-feeding, ask your doctor or pharmacist for advice before taking Trazodone Oral Solution.

### Driving and using machines

Trazodone Oral Solution may make you feel drowsy, therefore care should be taken when driving or operating machinery.

**Do not** drive or use machines if you feel dizzy, sleepy, or your coordination is affected.

### Important information about some of the other ingredients in Trazodone Oral Solution

Your medicine contains:

- **Sodium saccharin and sodium citrate** – this medicinal product contains 0.13mmol (or 3mg) sodium per 5ml spoonful. To be taken into consideration by patients on a controlled sodium diet.

- **Sorbitol (E420)** - if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
3. How to take Trazodone Oral Solution

Always take Trazodone Oral Solution exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- Your doctor may tell you to take your medicine either in divided doses, after food, or as a single dose before you go to bed.
- This medicine must not be mixed with other medicines.

**Adults**

- The usual starting dose is three 5ml spoonfuls (150mg trazodone hydrochloride) daily;
- this may be increased to six 5ml spoonfuls (300mg trazodone hydrochloride) daily;
- if you are in hospital you may be given a higher dose, of up to twelve 5ml spoonfuls (600mg trazodone hydrochloride) daily.

**Children**

- Trazodone Oral Solution should **not** be given to children.

**Elderly or frail**

- The usual starting dose is two 5ml spoonfuls (100mg trazodone hydrochloride) daily;
- this may be increased to a maximum of six 5ml spoonfuls (300mg trazodone hydrochloride) daily.

It may take 1 to 2 weeks of treatment before you begin to feel better. This is normal for this type of medicine. Your doctor should ask to see you 3 to 4 weeks after you start taking your medicine. If you do not feel any better, tell your doctor.

You must continue to take your medicine for as long as the doctor tells you to even if you feel better; this may be for several months after you start to feel better.

**Do not** stop taking Trazodone Oral Solution suddenly. Your doctor will tell you how to reduce your dose gradually.

**If you take more Trazodone Oral Solution than you should**

- If you take more Trazodone Oral Solution than your doctor has told you to, contact your nearest hospital or casualty department immediately and take your Trazodone Oral Solution with you.

**If you forget to take Trazodone Oral Solution**

- If you forget to take a dose, do not worry. Take the next dose when it is due.
- **Do not** take double the amount to make up for a forgotten dose.
4. Possible side effects
Like all medicines, Trazodone Oral Solution can cause side effects, although not everybody gets them.

If you have any of the following side effects while taking your medicine tell your doctor immediately or go to hospital straight away:

- **thoughts of suicide and worsening of your depression or anxiety disorder.** If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks, but sometimes longer.

  You may be more likely to think like this:
  - If you have previously had thoughts about killing or harming yourself.
  - If you are a young adult. Information from clinical trials has shown an increased risk in suicidal behaviour in young adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, **contact your doctor or go to a hospital straight away.**

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

- **Severe allergic reaction which may include a red and lumpy skin rash, difficulty breathing, swelling of eyelids, face, lips, mouth or tongue, unexplained high temperature (fever) and feeling faint. If the swelling affects your throat and makes breathing and swallowing difficult, go to hospital straight away.**

- You have convulsions or fits.
- You feel agitated, confused, restless, sweating, shaking, shivering, hallucinating (experiencing strange visions or sounds), sudden jerks of the muscles, a fast heartbeat, high temperature (fever). You may have a condition called Serotonin Syndrome.
- You have a high temperature (fever), sweating, changes in your blood pressure, a feeling of being dazed or almost unconscious and muscle stiffness. You may have a rare condition called Neuroleptic Malignant Syndrome.
- You have concentrated urine (dark in colour), feel or are sick, muscle cramps, confusion and fits. You may have a condition called hyponatraemia.
- You get infections more easily than normal, you bruise more easily than normal, or you start to suffer from tiredness.
weakness, or feel faint and dizzy. You may have certain blood disorders.
• Yellowing of the skin and whites of the eyes (jaundice). This could mean that your liver is not working properly.
• Some men have experienced long-lasting and painful erections with trazodone. If this happens to you it is important that you stop taking your medicine and tell your doctor immediately.

Other possible side effects:
• you may feel sleepy when you first start taking Trazodone Oral Solution. This should wear off as you continue to take the oral solution.
• dizziness
• headache
• feeling or being sick
• weakness
• feeling less alert
• weight loss
• shaking (tremors)
• dry mouth
• slow or fast heart beat
• low blood pressure (leading to fainting or feeling dizzy) when you stand up or sit up after lying down
• swelling (fluid retention)
• constipation
• diarrhoea
• blurred vision
• feeling restless
• becoming confused
• difficulty in falling asleep
• skin rash

See section 2 of this leaflet for side effects that may be caused by some of the ingredients in your medicine (Important information about some of the other ingredients in Trazodone Oral Solution).

If you have any other symptoms that you do not understand, tell your doctor or pharmacist.

5. How to store Trazodone Oral Solution
Keep out of the reach and sight of children.
Do not use after the expiry date stated on the carton and bottle label. The expiry date refers to the last day of that month.
Do not store above 25°C.
Keep bottle in the outer carton in order to protect from light.

**Once opened, use within one month.**

Do not use if you notice any visible signs of damage to the bottle or deterioration in your medicine. Return it to your pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines that have passed the expiry date or have been open for more than one month. These measures will help to protect the environment.

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### 6. Further information

**What Trazodone Oral Solution contains**

- The active substance is trazodone hydrochloride. Each 5ml of Trazodone Oral Solution contains 50mg of trazodone hydrochloride.

- The other ingredients are benzoic acid, sodium saccharin, hypromellose, sorbitol (E420), glycerol, orange flavour, citric acid monohydrate, sodium citrate and purified water (see section 2, Before you take Trazodone Oral Solution).

**What Trazodone Oral Solution looks like and contents of the pack**

Trazodone Oral Solution is a colourless to yellowish clear solution with an orange odour. It is available in an amber glass bottle containing 120ml of medicine.

**Marketing Authorisation Holder**

Focus Pharmaceuticals Limited, Unit 5, Faraday Court, First Avenue, Centrum 100, Burton upon Trent, Staffordshire, DE14 2WX, UK

Tel: 01283 495 280  Fax: 01283 495 290

Email: medinfo@focuspharma.co.uk

**Manufacturer**

HELP S.A., Pedini Ioannina, 45500 Ioannina, Greece.

Or

P. N. G. Gerolymatos S.A. Plant B, 4 Asklepiaou Str., 145 68 Kryoneri, Athens, Greece.

For any information about this medicinal product, please contact the Marketing Authorisation Holder, details provided above.

For information in large print, audio CD or Braille please telephone 01283 495 280 or email medinfo@focuspharma.co.uk.

This leaflet was last approved in March 2011.
Module 4

Labelling

Carton with braille
Bottle label

Each 5ml of oral solution contains 50mg trazodone hydrochloride. Also contains sorbitol and sodium. See leaflet for further information.

For oral use.
Take as directed by your doctor.
Do not store above 25°C.
Keep bottle in the outer carton to protect from light.
Once opened, use within 1 month.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Focus Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Trazodone Hydrochloride 50mg/5ml Oral Solution (PL 20046/0073, UK/H/2027/01/DC) on 23rd March 2011. The product is a prescription-only medicine.

This is a generic application for Trazodone Hydrochloride 50mg/5ml Oral Solution, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK reference product, Molipaxin™ Liquid 50mg/5ml, originally licensed to Sanofi-aventis (PL 00109/0117) on 6th January 1983. The reference licence has undergone Change of Ownership (CoA) procedures and was authorised to the current MA Holder, Winthrop Pharmaceuticals UK Limited (PL 17780/0542) on 27th October 2010. The reference product has been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in this Decentralised Procedure, Focus Pharmaceuticals Limited applied for a Marketing Authorisation for Trazodone Hydrochloride 50mg/5ml Oral Solution in Ireland.

Trazodone Hydrochloride 50mg/5ml Oral Solution is indicated for the relief of symptoms in all types of depression including depression accompanied by anxiety. Symptoms of depression likely to respond in the first week of treatment include depressed mood, insomnia, anxiety, somatic symptoms and hypochondriasis.

Trazodone (ATC code – N06A X05) is a triazolopyridine derivative which differs chemically from other currently available antidepressants. Although trazodone bears some resemblance to the benzodiazepines, phenothiazines and tricyclic antidepressants, its pharmacological profile differs from each of these classes of drugs. The basic idea for the development of trazodone was the hypothesis that depression involves an imbalance of the mechanism responsible for the emotional integration of unpleasant experiences. Consequently, new animal models of depression consisting of responses to unpleasant or noxious stimuli, instead of the current tests related to the aminergic theory of depression, were used in studying the drug. Trazodone inhibits serotonin uptake into rat brain synaptosomes and by rat platelets at relatively high concentrations and inhibits brain uptake of noradrenaline in vitro only at very high concentrations. It possesses antiserotonin-adrenergic blocking and analgesic effects. The anticholinergic activity of trazodone is less than that of the tricyclic antidepressants in animal studies and this has been confirmed in therapeutic trials in depressed patients.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that this was a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for an oral solution.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities.
as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The excipients used in the product formulation are commonly used pharmaceutical compounds. There are no environmental concerns associated with the method of manufacture or formulation of the product.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Trazodone Hydrochloride 50mg/5ml Oral Solution</th>
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<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Trazodone hydrochloride</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other antidepressants (N06A X05)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Oral solution 50 mg/5 ml</td>
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<tr>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20046/0073</td>
</tr>
</tbody>
</table>
| Name and address of the authorisation holder     | Focus Pharmaceuticals Limited  
Unit 5, Faraday Court  
First Avenue  
Centrum 100  
Burton upon Trent  
Staffordshire  
DE14 2WX |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Trazodone hydrochloride

Nomenclature:

INN: Trazodone hydrochloride

Chemical names:  
  i) 2-[3-[4-(m-Chlorophenyl)-1-piperazinyl]propyl]-s-triazolo[4,3-a]pyridin-3(2H)-one hydrochloride  
  ii) 2-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl}-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one hydrochloride

Structure:

Molecular formula:  C$_{19}$H$_{23}$Cl$_{2}$N$_{5}$O

Molecular weight:  408.33 g/mol

CAS No:  25332-39-2

Physical form:  A white or almost white, crystalline powder

Solubility:  Soluble in water, sparingly soluble in ethanol (96%), practically insoluble in ether

The active substance, trazodone hydrochloride, is the subject of a British Pharmacopeia (BP) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer.

The active substance is stored in appropriate packaging. Satisfactory specifications have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended) and is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the 5-year retest period that has been applied.
MEDICINAL PRODUCT

Description and Composition
Trazodone Hydrochloride 50mg/5ml Oral Solution is presented in amber glass bottles as a colourless to yellowish, clear solution with an orange odour. Each 5 ml of solution contains 50 mg of the active ingredient, trazodone hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely benzoic acid, saccharin sodium, hypromellose, liquid sorbitol (non-crystallising), glycerol, orange flavour, citric acid monohydrate, sodium citrate and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of orange flavour, which complies with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms.

Pharmaceutical development
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a generic version of the reference product, Molipaxin™ Liquid 50mg/5ml (PL 17780/0542, Winthrop Pharmaceuticals UK Limited).

Comparative impurity data were provided for batches of the test and reference products. The impurity profiles were satisfactory.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted on pilot and production scale batches and the results were satisfactory. The applicant has committed to complete/perform process validation studies on full-scale commercial-scale batches.

Finished product specifications
The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
The oral solution is licensed for marketing in 125 ml amber, type III glass bottles, sealed with high density polyethylene (HDPE) tamper evident closures, containing 120ml of solution. The bottles are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons.
Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging components comply with relevant Ph. Eur. requirements and satisfy EU legislation, Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months has been set for the unopened bottle; once opened, the contents of the bottle should be used within 1 month; this is satisfactory. Storage instructions are ‘Do not store above 25°C. Keep the bottle in the outer carton to protect from light’.

**Bioequivalence Study**

A bioequivalence study is not necessary to support this application for an oral solution.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The labelling fulfils the statutory requirements for Braille.

PIL user testing has been accepted based on a bridging report provided by the applicant. The bridging is accepted.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Trazodone Hydrochloride 50mg/5ml Oral Solution from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that this is an application for a generic version of a product that has been licensed for more than 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of trazodone hydrochloride, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference product, Molipaxin™ Liquid 50mg/5ml (Winthrop Pharmaceuticals UK Limited).

There are no objections to approval of Trazodone Hydrochloride 50mg/5ml Oral Solution from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS
Trazodone Hydrochloride 50mg/5ml Oral Solution is indicated for the relief of symptoms in all types of depression including depression accompanied by anxiety. Symptoms of depression likely to respond in the first week of treatment include depressed mood, insomnia, anxiety, somatic symptoms and hypochondriasis.

The indications are consistent with those for the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY
The toxicology of trazodone hydrochloride is well-known. No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY
The clinical pharmacology of trazodone hydrochloride is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Clinical efficacy
No new data are submitted and none are required for these types of application. Efficacy is reviewed in the clinical overview. The efficacy of trazodone hydrochloride is well-established from its extensive use in clinical practice.

No bioequivalence studies are provided or required, as justified by the applicant in accordance with the requirements of (CPMP/EWP/QWP/1401/98).

Clinical safety
No new safety data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of trazodone hydrochloride is well-known.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.

Product Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory. The PIL user testing has been evaluated and is accepted.

Labelling

The labelling is satisfactory.

Clinical overview

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS

For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference product, Molipaxin™ Liquid 50mg/5ml (Winthrop Pharmaceuticals UK Limited).

Sufficient clinical information has been submitted to support this application. All issues have been adequately addressed by the applicant. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Trazodone Hydrochloride 50mg/5ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview.

The applicant’s Trazodone Hydrochloride 50mg/5ml Oral Solution has been demonstrated to be a generic version of the reference product, Molipaxin™ Liquid 50mg/5ml (PL 17780/0542; Winthrop Pharmaceuticals UK Limited). Bioequivalence studies are not necessary to support this application for an oral solution.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for the UK reference product and is satisfactory.

The PIL is in line with the SmPC and is satisfactory. PIL user testing has been accepted, based on a bridging report provided by the applicant making reference to a successfully user-tested parent PIL. The results show that the leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The bridging is accepted.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Trazodone Hydrochloride 50mg/5ml Oral Solution is a generic version of the UK reference product, Molipaxin™ Liquid 50mg/5ml (Winthrop Pharmaceuticals UK Limited). Extensive clinical experience with trazodone hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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