Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Molipaxin 100 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100mg trazodone hydrochloride.

Excipients
Contains 159.0 mg lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard.

Product imported from the UK:
Size No. 2 opaque violet/fawn hard gelatin capsules having the code "R365C" imprinted on one piece, the Roussel logo on the other piece and containing a white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For oral administration.

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

4.2 Posology and method of administration

Recommended Dosage

Adults Only:

According to severity, treatment should be initiated at 75 to 150mg per day as a single evening dose and then increased to 200 or 300mg per day, respectively, at the end of the first week. In hospitalised patients with exceptionally severe depression, dosage may be further increased to a maximum of 600mg per day in divided doses.

The Elderly:

In elderly and frail patients, the recommended starting dosage is 100mg in divided doses or in a single dose to be administered at bedtime, increasing thereafter according to clinical progress. In general, single doses above 100mg should be avoided in these patients. It is unlikely that doses higher than 300mg will be exceeded.

Children:

There is insufficient data to recommend the use of Molipaxin in children and adolescents under the age of 18 (see section 4.4).

Hepatic Impairment:
Trazodone undergoes extensive hepatic metabolism, see section 5.2, and has also been associated with hepatotoxicity, see sections 4.4 and 4.8. Therefore caution should be exercised when prescribing for patients with hepatic impairment, particularly in cases of severe hepatic impairment. Periodic monitoring of liver function may be considered.

Renal Impairment:
No dosage adjustment is usually necessary, but caution should be exercised when prescribing for patients with severe renal impairment (see also section 4.4 and 5.2).

4.3 Contraindications

Known sensitivity to Trazodone or any of the excipients.
Pregnancy (see Section 4.6).
Alcohol intoxication and intoxication with hypnotics.
Acute myocardial infarction.

4.4 Special warnings and precautions for use

Use in children and adolescents under the age of 18
Trazodone should not be used in the treatment of depression in children and adolescents under the age of 18 years. Studies with other classes of antidepressants have shown a risk of suicidality, self-harm and hostility to be related to the compounds. This risk cannot be excluded in Trazodone. Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

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 Molipaxin 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 close 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 these symptoms persist.

To minimise the potential risk of suicide attempts, particularly at therapy initiation, only restricted quantities of trazodone should be prescribed at each occasion.
It is recommended that careful dosing and regular monitoring is adopted in patients with the following conditions:

- Epilepsy, specifically abrupt increases or decreases of dosage should be avoided
- Patients with hepatic or renal impairment, particulary if severe
- Patients with cardiac disease, such as angina pectoris, conduction disorders or AV blocks of different degree, recent myocardial infarction
- Hyperthyroidism

- Micturition disorders, such as prostate hypertrophy, although problems would not be anticipated as the anticholinergic effect of trazodone is only minor
- Acute narrow angle glaucoma, raised intra-ocular pressure, although major changes would not be anticipated due to the minor anticholinergic effect of trazodone
  Should jaundice occur in a patient, trazodone therapy must be withdrawn.

Administration of antidepressants in patients with schizophrenia or other psychotic disorders may result in a possible worsening of psychotic symptoms. Paranoid thoughts may be intensified. During therapy with trazodone a depressive phase can change from a manic –depressive psychosis into a manic phase. In that case trazodone must be stopped.

Interactions in terms of serotonine syndrome/malignant neuroleptic syndrome have been described in case of concomitant use of other serotonergically acting substances like other antidepressants (e.g. tricyclic antidepressants, SSRI's, SNRI's and MAO-inhibitors) and neuroleptics. Malignant neuroleptic syndromes with fatal outcome have been reported in cases of coadministration with neuroleptics, for which this syndrome is a known possible adverse drug reaction. See Sections 4.5 and 4.8 for further information.

Since agranulocytosis may clinically reveal itself with influenza-like symptoms, sore throat, and fever, in these cases it is recommended to check haematology.

Hypotension, including orthostatic hypotension and syncope, has been reported to occur in patients receiving trazodone. Concomitant administration of antihypertensive therapy with trazodone may require a reduction in the dose of the antihypertensive drug.

Elderly patients are often more sensitive to antidepressants, in particular to orthostatic hypotension and other anticholinergic effects.

Following therapy with trazodone, particularly for a prolonged period, an incremental dosage reduction to withdrawal is recommended, to minimise the occurrence of withdrawal syptoms, characterised by nausea, headache, and malaise.

There is no evidence that trazodone hydrochloride possesses any addictive properties.

As with other antidepressant drugs, cases of QT interval prolongation have been reported with trazodone very rarely. Caution is advised when prescribing trazodone with medicinal products known to prolong QT interval. Trazodone should be used with caution in patients with known cardiovascular disease including those associated with prolongation of the QT interval.

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

As with other drugs with alpha-adrenolytic 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.

Undesirable effects may be more common during concomitant use of trazodone and herbal preparations containing St. John's wort (Hypericum perforatum).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase defieiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

General: The sedative effects of antipsychotics, hypnotics, sedatives, anxiolytics, and antihistaminic drugs may be intensified; dosage reduction is recommended in such instances.

The metabolism of antidepressants is accelerated due to hepatic effects by oral contraceptives, phenytoin, carbamazepine and barbiturates. The metabolism of antidepressants is inhibited by cimetidine and some other antipsychotics.

CYP3A4 inhibitors: Drug metabolism studies in vitro are indicative 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. It has been confirmed in in- vivo-studies in healthy volunteers, that a ritonavir dose of 200 mg BID increased the plasma levels of trazodone by greater than twofold, leading to nausea, syncope and hypotension. If trazodone is used with a potent CYP3A4 inhibitor, a lower dose of trazodone should be considered. However, coadministration of trazodone and potent CYP3A4 inhibitors should be avoided where possible.

Carbamazepine: Coadministration results in reduced plasma concentrations of trazodone. Concomitant use of carbamazepine 400 mg daily led to a decrease of plasma concentrations of trazadone and its active metabolite m-chlorophenylpiperazine of 76 % and 60 %, respectively. Patients should be closely monitored to ascertain if an increased trazodone dosage is required.

Tricyclic antidepressants: concurrent administration should be avoided due to the risk of interaction. Serotonine syndrome and cardiovascular side effects should be bewared.

Fluoxetine: rare cases have been reported of elevated trazodone plasma levels and adverse effects when trazodone had been combined with fluoxetine, a CYP1A2/2D6 inhibitor. The mechanism underlying a pharmacokinetic interaction is not fully understood. A pharmacodynamic interaction (serotonine syndrome) could not be excluded.

Monoamine oxidase inhibitors: Possible interactions with monoamine oxidase inhibitors have occasionally been reported. Although some clinicians do give both concurrently, use of trazodone concomitantly with MAOIs, or within two weeks from discontinuation of these substances, is not recommended. The administration of MAOIs within one week since discontinuation of trazodone treatment is not recommended either.

Phenothiazines: Severe orthostatic hypotension has been observed in case of concomitant use of phenothiazines, like e.g. chlorpromazine, fluphenazine, levomepromazine, perphenazine.

Anaesthetics/muscle relaxants: Trazodone hydrochloride may enhance the effects of muscle relaxants and volatile anaesthetics, and caution should be exercised in such instances.

Alcohol: Trazodone intensifies the sedative effects of alcohol. Alcohol should be avoided during trazodone therapy.

Levodopa: Antidepressants can accelerate the metabolism of levodopa.

Other
Concomitant use of Trazodone with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Caution should be used when these drugs are coadministered with 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.

Undesirable effects may be more frequent when trazodone is administered together with preparations containing Hypericum perforatum.

There have been reports of changes in prothrombin time in patients concomitantly receiving trazodone and warfarin.

Concurrent use with trazodone may result in elevated serum levels of digoxin or phenytoin.

Monitoring of serum levels should be considered in these patients.

4.6 Fertility, pregnancy and lactation

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

Pregnancy:
Data on a limited number (< 200) of exposed pregnancies indicate no adverse effects of trazodone on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data area available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development at therapeutic doses (see section 5.3).
Caution should be exercised when prescribing to pregnant women. When trazodone is used until delivery, newborns should be monitored for the occurrence of withdrawal symptoms.

Lactation:
Limited data indicate that excretion of trazodone in human breast milk is low, but levels of the active metabolite are not known. Due to the paucity of data, a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with trazodone should be made taking into account the benefit of breast-feeding to the child and the benefit of trazodone therapy to the woman.

4.7 Effects on ability to drive and use machines

Trazodone has minor or moderate influence on the ability to drive and use machines.
Patients should be cautioned against the risks of driving or operating machinery until they are sure they are not affected by drowsiness, sedation, dizziness, confusional states, or blurred vision.

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).

The following symptoms, some of which are commonly reported in cases of untreated depression, have also been recorded in patients receiving trazodone therapy.

MedDRA System Organ Class	**Frequency not known (cannot be estimated from the available data)**
Blood and the lymphatic system disorders	Blood dyscrasias (including agranulocytosis, thrombocytopenia, eosinophilia, leucopenia and anaemia)
Immune system disorders Allergic reactions	Endocrine disorders Syndrome of Inappropriate Antidiuretic Hormone Secretion
Metabolism and nutrition disorders	Hyponatraemia[4], weight loss, anorexia, increased appetite,
Psychiatric disorders	Suicidal ideation or suicidal behaviours[5], confusional state, insomnia, disorientation, mania, anxiety, nervousness, agitation (very occasionally exacerbating to delirium), delusion, aggressive reaction, hallucinations, nightmares, libido decreased, withdrawal syndrome

Nervous system disorders	Serotonin syndrome, convulsion, neuroleptic malignant syndrome, dizziness, vertigo, headache, drowsiness[6], restlessness, decreased alertness, tremor, blurred vision, memory disturbance, myoclonus, expressive aphasia, paraesthesia, dystonia, taste altered
Cardiac disorders	Cardiac arrhythmias[7] (including Torsade de Pointes, palpitations, premature ventricular contractions, ventricular couplets, ventricular tachycardia), bradycardia, tachycardia, ECG abnormalities (QT prolongation)[2]
Vascular disorders	Ortostatic hypotension, hypertension, syncope
Respiratory, thoracic and mediastinal disorders	Nasal congestion, dyspnoea
Gastrointestinal disorders	Nausea, vomiting, dry mouth, constipation, diarrhoea, dyspepsia, stomach pain, gastroenteritis, increased salivation, paralytic ileus
Hepato-biliary disorders	Hepatic function abnormalities (including jaundice and hepatocellular damage)[8] , cholestasis intrahepatic
Skin and subcutaneous tissue disorders	Skin rash, pruritus, hyperhidrosis
Musculoskeletal and connective tissue disorders	Pain in limb, back pain, myalgia, arthralgia
Renal and urinary disorders	Micturition disorderd
Reproductive system and breast disorders	Priapism[9]
General disorders and administration site conditions	Weakness, oedema, influenza-like symptoms, fatigue, chest pain, fever
Investigations	Elevated liver enzymes

4. Fluid and electrolyte status should be monitored in symptomatic patients.
5. See also Section 4.4.
6. Trazodone is a sedative antidepressant and drowsiness, sometimes experienced during the first days of treatment, usually disappears on continued therapy.
7. 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.
8. Adverse effects on hepatic function, sometimes severe, have been rarely reported. Should such effects occur, trazodone should be immediately discontinued.
9. See also Section 4.4

4.9 Overdose

Features of toxicity
The most frequently reported reaction to overdose have included drowsiness, dizziness, nausea and vomiting. In more serious cases coma, tachycardia, hypotension, hyponatraemia, 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 1 g trazodone, or in children who have ingested more than 150 mg 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/bodyweight) or lorazepam (4mg in an adult and 0.5mg/kg in a child). 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, e.g. dopamine or dobutamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Molipaxin is a potent anti-depressant. It also has anxiety reducing activity. Molipaxin is a triazolopyridine derivative chemically unrelated to known tricyclic, tetracyclic and other anti-depressant agents. It has negligible effect on noradrenaline re-uptake mechanisms. Whilst the mode of action of Molipaxin is not known precisely, its anti-depressant 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 5-13 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.

In vitro studies in human liver microsomes show that Trazodone is mainly metabolized by cytochrome P4503A4 (CYP3A4).

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Gelatin
Titanium dioxide (E171)
Erythrosine (E127)

Indigo carmine (E132)
Red iron oxide (E172)
Yellow iron oxide (E172)

Printing Ink
Ink (1028 or 1014) Black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the Blister and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in a dry place

6.5 Nature and contents of container

PVdC coated 250 μm PVC blister pack sealed with 20 μm aluminium foil containing 56 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd July 2011

10 DATE OF REVISION OF THE TEXT