SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
   Trittico 75 mg prolonged-release tablets
   Trittico 150 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   **Trittico 75 mg prolonged-release tablets**
   Each tablet contains:
   75 mg trazodone hydrochloride corresponding to 68.3 mg trazodone

   **Trittico 150 mg prolonged-release tablets**
   Each tablet contains
   150 mg trazodone hydrochloride corresponding to 136.6 mg trazodone
   For complete list of excipients see section 6.1.

3. PHARMACEUTICAL FORM
   Scored prolonged-release dividable tablets.

4. CLINICAL PARTICULARS
   4.1 Therapeutic indications:
   Depressive disorders with or without anxiety

   4.2 Posology and method of administration:
   The use of the drug is restricted to adult patients.
   Therapy should begin with an evening administration and with increasing daily doses. The drug should be administered for therapeutic cycles of at least one month.
   Decrease of the side-effects (increase of the resorption and decrease of the peak plasma concentration) can be reached by taking trazodone hydrochloride after a meal.
   The scored tablets can be divided into three parts in order to permit a gradual dose increase depending on the severity of the disease, weight, age and general condition of the patient.

   **Adults**
   75-150 mg/day to be administered in a single dose in the evening before bedtime.
   The dose can be increased up to 300 mg/day divided in two administrations.
   In hospitalized patients the dose can be further increased up to 600 mg/day in repeated doses.

   **Elderly:**
   For very elderly, or frail patients, the recommended initial dose is reduced to 100 mg a day, administered in divided doses or as a single night time dose (See Section 4.4). This may be incrementally increased, as described under Adults, under supervision, according to tolerance and efficacy. In general, single doses above 100 mg should be avoided in these patients. . It is unlikely that doses higher than 300 mg/day will be exceeded.

   **Children:**
   Use of trazodone is not recommended in children and adolescents under 18 due to a lack of data on safety.

   **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 Contra-indications
   Known hypersensitivity to trazodone and any of the excipients.
   Trittico is generally contraindicated in pregnancy and lactation (see section 4.6)
   Alcohol intoxication and intoxication with hypnotics.
   Acute myocardial infarction.
4.4 Special warnings and special precautions for use

Use in children and adolescents under 18

Trazodone should not be used in children and adolescents under 18. Suicidal behaviour (suicidal attempt and suicidal planning) and hostility (essentially aggressiveness, opposing behaviour and anger) has been observed in clinical study on children and adolescents treated with antidepressant more frequently than with placebo. Moreover, long-term safety data on children and adolescents regarding 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.

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 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 these symptoms present.

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, particularly 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 serotonin 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 co-administration 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:

Elderly patients are more often more sensitive to antidepressants, in particular may more often experience to orthostatic hypotension, somnolence, and other anticholinergic effects of trazodone. Careful consideration should be given to the potential for additive effects with concomitant medication use such as with other psychotropics or antihypertensives or in the presence of risk factors such as comorbid disease, which may exacerbate these reactions. It is recommended that the patient/carer is informed of the potential for these reactions and monitored closely for such effects following initiation of therapy, prior to and following upward dose titration.

Following therapy with trazodone, particularly for a prolonged period, an incremental dosage reduction to withdrawal is recommended, to minimise the occurrence of withdrawal symptoms, 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-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.
Important information on some excipients
Trittico prolonged-release tablets contain saccharose: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency, should not take this medicine.

4.5 Interaction with other medicaments 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 the inhibitors of cytochrome P4503A4 (CYP3A4), such as erythromycin, ketoconazole, itraconazole, ritonavir, indinavir and nefazodone. It is likely that 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 two-fold, leading to nausea, syncope and hypotension. Therefore, if trazodone is used with a potent CYP3A4 inhibitor, a lower dose of trazodone should be considered. However, co-administration of trazodone and potent CYP3A4 inhibitors should be avoided where possible.

Carbamazepine
Coadministration of carbamazepine in association with trazodone results in reduced plasma concentrations of trazodone. Concomitant use of carbamazepine 400 mg daily led to a decrease of plasma concentrations of trazodone 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. Serotonin syndrome and cardiovascular side effects should be beware.

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 (serotonin syndrome) could not be excluded.

Monoamine oxidase inhibitors (MAOIs)
Possible interactions with monoamine oxidase inhibitors (MAOIs) 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.

Phenothiazine
Severe orthostatic hypotension has been observed in case of concomitant use of phenothiazine, 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 co-administered 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 a 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 Pregnancy and lactation

**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 the ability to drive and to 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.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Blood dyscrasias (including agranulocytosis, thrombocytopenia, eosinophilia, leucopenia and anaemia)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Syndrome of Inappropriate Antidiuretic Hormone Secretion</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatraemia¹, weight loss, anorexia, increased appetite,</td>
</tr>
<tr>
<td></td>
<td>Suicidal ideation or suicidal behaviours², confusional state, insomnia, disorientation, mania, anxiety, nervousness, agitation (very occasionally exacerbating to delirium), delirium, aggressive reaction, hallucinations, nightmares, libido decreased, withdrawal syndrome</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Serotonin syndrome, convulsion, neuroleptic malignant syndrome, dizziness, vertigo, headache, drowsiness³, restlessness, decreased alertness, tremor, blurred vision, memory disturbance, myoclonus, expressive aphasia, paraesthesia, dystonia, taste altered</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac arrhythmias⁴ (including “Torsade de Pointes”, palpitations, premature ventricular contractions, ventricular couplets, ventricular tachycardia), bradycardia, tachycardia, ECG abnormalities (QT prolongation)⁵</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Orthostatic hypotension, hypertension, syncope</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal congestion, dyspnoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting, dry mouth, constipation, diarrhoea, dyspepsia, stomach pain, gastroenteritis, increased salivation, paralytic ileus</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Hepatic function abnormalities (including jaundice and hepatocellular damage)⁶, cholestasis intrahepatic</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin rash, pruritus, hyperhidrosis</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in limb, back pain, myalgia, arthralgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Micturition disordered</td>
</tr>
</tbody>
</table>

¹ Fluid and electrolyte status should be monitored in symptomatic patients.
² See also Section 4.4.
³ Trazodone is a sedative antidepressant and drowsiness, sometimes experienced during the first days of treatment, usually disappears on continued therapy.
⁴ 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.
⁵ Adverse effects on hepatic function, sometimes severe, have been rarely reported.
⁶ See also Section 4.4.
Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national system of reporting at web site www.agenziafarmaco.gov.it/it/responsabili.

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, hypotension, hyponaeraemia, convulsions and respiratory failure have been reported. Cardiac features may include bradycardia, QT prolongation and torsade de pointes. Symptoms may appear within 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 Glasgow Coma Scale (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 (0.1-0.3 mg/kg body weight) or lorazepam (4 mg in an adult and 0.05 mg/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, e.g. dopamine or dobutamine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacodynamic properties: psychoanaleptic, anti-depressive.
ATC code: N06AX05
Trazodone is a trazolopiridine derivative which is effective in the treatment of depressive disturbances, including depression associated with anxiety and sleep disturbances (ATC code: N06AX05) and characterized by a short onset of action (about a week).
Trazodone is an inhibitor of serotonin re-uptake and an antagonist of 5-HT2 receptors, the activation of which is commonly associated with symptoms such as anxiety, psychomotor agitation and changes in sexual function. Unlike other psychotropic drugs, trazodone is not contraindicated in glaucoma and in urinary disturbances, it does not have extrapyramidal effects and does not potentiate adrenergic transmission; because it is devoid of anticholinergic activity, trazodone does not have the typical effects of tricyclic antidepressants on heart function.

5.2 Pharmacokinetic properties
After a single oral dose administration of 75 mg prolonged-release trazodone, a Cmax of around 0.7 µg/ml is reached with a Tmax at 4 hours after administration and an AUC of around 8 µg/ml/h. After a single oral dose of 150 mg prolonged-release trazodone, a Cmax of about 1.2 µg/ml is reached with a Tmax 4 hours after administration. Half-life is around 12 hours and AUC around 18 µg /ml/h.
In vitro studies in human liver microsomes show that trazodone is mainly metabolized by cytochrome P4503A4 (CYP3A4).

5.3 Preclinical safety data

Acute toxicity: The LD50 of trazodone by the oral route is 610 mg/kg in the mouse, 486 mg/kg in the rat and 560 mg/kg in the rabbit. The effects observed consisted of sedation, salivation, palpebral ptosis and clonic convulsions.
Repeated toxicity: Subchronic studies were carried out in the rat, rabbit and dog and chronic studies in the rat, dog and monkey. The oral doses administered ranged between 15 and 450 mg/kg/die in the rat, 15 and 100 mg/kg/die in the rabbit, 3 and 100 mg/kg/die in the dog, and 20 and 80 mg/kg/die in the monkey. In the rat studies treatment caused hypertrophy of the hepatocytes and smooth endoplasmic reticulum with consequent hepatomegaly. This effect is the result of a detoxification mechanism and cannot be interpreted as a pathologic event. Furthermore, lethal doses also produced effects already observed in acute toxicity studies. The relevant NOEL (No Observed Adverse Effect Level) was 30 mg/kg/die. In the rabbit only CNS-depressant effects were observed with a relative NOEL of 50 mg/kg/die. In the dog, the symptoms already observed with acute intoxication were worsened with repeated administrations and the relevant NOEL was 10 mg/kg/die. The monkey appeared to be more resistant than the dog presenting only pharmacodynamic disturbances. The NOEL was 20 mg/kg/die.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Priapism</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Weakness, oedema, influenza-like symptoms, fatigue, chest pain, fever</td>
</tr>
<tr>
<td>Investigations</td>
<td>Elevated liver enzymes</td>
</tr>
</tbody>
</table>
Reproduction toxicity. No effects on fertility were observed in the rat up to the dose of 300 mg/kg/die. Teratogenicity studies in the rat showed an increase in embryolethal effects only at doses that are toxic on the maternal organism (300–450 mg/kg/die). In the rabbit, embryolethal effects and rare cases of congenital anomalies were observed only at toxic doses in the mothers (210–450 mg/kg/die). The lack of direct effects on the embryo is confirmed by studies performed in the rat on the placental passage of trazodone: only negligible concentrations of the drug were observed in the embryonic tissues and amniotic liquid. Peri- and post-natal studies in the rat showed only a reduction in the body weight increase of pups at doses over 30 mg/kg/die.

Mutagenicity. In vitro mutagenicity tests (in bacterial cells, V77 cells of Chinese hamsters, in murine lymphoma cells, chromosomal aberrations in CHO, CHL/IU cells and human lymphocytes) and in vivo mutagenicity tests (micronucleus test in the mouse and analysis of the chromosomal metaphase in the rat) did not show any mutagenic effects.

Carcinogenic potential. Studies carried out in the mouse and rat did not reveal any potential risk of tumors.

Antigenicity. Trazodone showed to be devoid of antigenic activity.

Cardiotoxicity. The cardiovascular effects of trazodone were studied in the rat, guinea-pig, cat and dog. The drug showed an almost total lack of cardiotoxicity since no variations in ECG tracings were observed at non hypotensive doses.

Hormonal effects. Single doses over 20 mg/kg administered intraperitoneally in the female rat caused a mild increase in prolactin. This effect disappeared with chronic administrations in the diet.

Drug dependence. Two studies performed in the rat excluded any potential drug-dependent effects.