SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trazodon HCl Sandoz 100 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of trazodone hydrochloride.

Excipient with known effect
Each tablet contains 160.75 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Oblong off-white tablets, with three scorelines. The tablet is about 18.5 mm long and about 6.7 mm wide.
The tablet can be divided into equal doses if broken in the middle, into a threequarter and a quarter tablet, if broken at an end scoreline, or into equal quarters if broken at all three scorelines.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Nationally completed name] is indicated for major depressive episode.

4.2 Posology and method of administration

For oral use.

Adults:

The optimum dosage should be individually determined for each patient.

The initial dose is 150 mg a day, administered in divided doses after food, or as a single dose upon retiring.

The dose will be increased every 3 to 4 days by 50 mg a day (preferably upon retiring) until an optimal therapeutic effect is achieved.

This may be increased up to a dose of 400 mg a day, administered in divided doses after food, or as a single dose upon retiring. In administering divided doses the major part of the divided dose should be taken upon retiring.

In hospitalised patients, the maximum daily dose may be incrementally increased to a maximum of 600 mg per day, administered as divided doses.

After reaching an effective dosage, clinical response is usually evident within two to four weeks. In the case of non – responders the dosage may be increased to the maximimum recommended. If, following this, there is no response after two to four weeks, therapy should be discontinued.

After reaching a satisfactory clinical response, the dosage should be maintained for a minimum of four weeks. Following this period, generally the dosage can be incrementally decreased, depending on therapeutic response . Patients should be maintained on the lowest effective dose and be periodically reassessed to determine the continued need for maintenance treatment.

In general it is preferable to continue therapy until the patient has been symptomless for four to six months; thereafter the dosage can be incrementally reduced until withdrawal is achieved.

Older people:

For very old, or frail people, 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 a dose of 300 mg per day will be exceeded.

Paediatric population:

[Nationally completed name] is not recommended for use in children below the age of 18 years due to a lack of data on safety and / or efficacy.

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 should 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).

Method and duration of use

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 tablets should be taken together with sufficient liquid (e.g. 1 glass of water) directly after a meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Alcohol intoxication and intoxication with hypnotics.
Acute myocardial infarct.

4.4 Special warnings and precautions for use

Warnings:

Paediatric population

Trazodone should not be used in the treatment of children and adolescents under the age of 18 years. Suicide related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressant compared to those treated with placebo. In addition, 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.

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 a 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 anti-depressants 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 attempt, particularly at therapy initiation, only restricted quantities of trazodone should be prescribed on 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 cardiovascular insufficienty, angina pectoris, conduction disorders or AV blocks of different degree, arrhythmias, recent myocardiac infarction, congenital long QT syndrome or bradycardia. Trazodone should be used with particular caution in these patients.
- Patients with hypokalaemia or hypomagneseia. These electrolyte-disturbances increase the risk for malignant arrhythmias and should be corrected before treatment with trazodone is started.
- 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 intro – 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.

Psychotic disorders

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 the dosage of trazodone must be stopped.

St. John's Wort

Side effects may occur with greater frequency during concomitant use of trazodone and phytotherapeutic remedies containing St. John's Wort (*Hypericum perforatum*).

Serotonin syndrome/malignant neuroleptic syndrome

Interactions in terms of serotonin syndrome / malignant neuroleptic syndrome have been described in case of concomitant use of other serotonergically acting substances like other antidepressanta (e.g. tricyclin antidepressants, SSRI's, SNRI's and MAO-inhibitors) triptans and neuroleptics. Malignant neuroleptic syndromes with fatal outcome have been reported in case of coadministration with neuroleptics, for which this syndrome is a known possible adverse drug reaction. (See Sections 4.5 and 4.8). Treatment with trazodone must be stopped immediately.

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.

Older people may more often experience 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.

Trazodone is a sedative antidepressant and causes drowsiness, especially at the beginning of treatment (see Sections 4.7 and 4.8)
Following therapy with trazodone, partiucularly 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.

Cases of QT interval prolongation have been reported with trazodone (see Section 4.8). Caution is advised when prescribing trazodone with medicinal products known to prolong QT interval such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine). 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 additional 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.

[Nationally completed name] contains sodium and lactose
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose maladsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

General:
The sedative effects of antipsychotics, hypnotics, sedatives, anxiolytics, and antihistaminic medicinal products may be intensified; dose 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 more than two-fold, leading to nausea, syncope and hypotension. If trazodone hydrochloride 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: Co administration 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.
Note that Serotonin syndrome and cardiovascular side effects may result from such concurrent administration.

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 the pharmacokinetic interaction is not fully understood. A pharmacodynamic interaction (serotonin syndrome) could not be excluded.

Monoamine Oxidase Inhibitors (MAOI): 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 therapy is not recommended either.

Phenothiazines: Severe orthostatic hypotension has been observed in case of concomitant use of phenothiazines, 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 torsades de pointes. Caution should be used when these drugs are coadministered with trazodone.

Antihypertensives: 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 case of other types of antihypertensive drug, although no clinical interactions have been reported, the possibility of potentiation should be considered.

St. John's Wort: Undesirable effects may be more frequent when trazodone is administered together with preparations containing *Hypericum perforatum*.

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

Digoxin: Concurrent usage with trazodone may result in elevated serum levels of digoxin. Monitoring of serum levels should be considered in these patients.

Phenytoin: Concurrent usage with trazodone may result in elevated serum levels of phenytoin. Monitoring of serum levels should be considered in these patients.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are limited amounts of data (less than 200 pregnancy outcomes) from the use of trazodone in pregnant women. Data of exposed pregnancies indicate no adverse effects of trazodone on pregnancy or on the health of the foetus / newborn child. No other relevant epidemiological data are available. Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn

(PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.
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 also section 5.3). As a precautionary measure, it is preferable to avoid the use of trazodone during pregnancy. 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.

Breast-feeding:
It is unknown to what extent trazodone and its metabolites are excreted in human milk.
A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue / abstain from trazodone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother.

4.7 Effects on ability to drive and use machines

[Nationally completed name] 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, suicidal behaviours have been reported during trazodone treatment or early after treatment discontinuation (see section 4.4.)

The most frequently reported adverse reactions are: dizziness, drowsiness, fatigue, nervousness and dry mouth.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Some of the reported undesirable effects are themselves commonly reported

symptoms in cases of untreated depression, e.g. inhibition, dry mouth, constipation, tremor and dizziness.

The frequency is defined as: very common (> 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:
Rare: Blood dyscrasias, including agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, and anaemia.

Immune system disorders:
Common: Allergic reactions

Endocrine disorders:
Not known: Syndrome of Inappropriate Antidiuretic Hormone Secretion

Metabolism and nutrition disorders:
Common: Weight gain, anorexia and increased hunger
Uncommon: Weight loss
Not known: hyponatraemia[1)].

Psychiatric disorders
Very common: nervousness
Common: Expressive aphasia, confusional state, disorientation, mania, agitation (very occasionally exacerbating to delirium), aggressive reaction, hallucinations..
Not known: Worsening delusions, inhibition, anxiety, suicidal ideation and suicidal behaviours[2)], insomnia, nightmares, withdrawal syndrome

Nervous system disorders:
Very common: dizziness, drowsiness[3)]
Common: Tinnitus, headache, tremor.

Uncommon: serotonin syndrome[4)], convulsions.

Rare: Myoclonus.

Very rare: neuroleptic malignant syndrome.

Not known: vertigo, restlessness, decreased alertness, memory disturbance, paraesthesia, dystonia..

Eye disorders:

Common: Accommodation and vision disorders, sometimes glaucoma, ocular pruritus, blurred vision

Cardiac disorders:

Common: Palpitation[5)], bradycardia, tachycardia.

Not known: cardiac arrhythmias[6)] (including Torsade de Pointes, premature ventricular couplets, ventricular tachycardia), ECT abnormalities (QT prolongation).

Vascular disorders:

Common: Orthostatic hypotension, hypertension, syncope

Respiratory, thoracic and mediastinal disorders

Common:: Nasal / sinal congestion.

Uncommon: dyspnoea

Gastrointestinal disorders:

Very common: dry mouth

Common: Taste changes, flatulence, nausea, vomiting, constipation and diarrhoea, dyspepsia, stomach pain, gastroenteritis.

Not known: Intestinal perforation, paralytic ileus, gastrointestinal spasm, and hiatus hernia, increased salivation.

Hepato-biliary disorders:

Rare: hepatic function abnormalities (including jaundice and hepatocellular damage)[7)]

Not known: Intrahepatic cholestasis.

Skin and subcutaneous tissue disorders:

Common: Skin rash, pruritus

Not known: hyperhidrosis

Musculoskeletal and connective tissue disorders:

Common: Asthenia, chest pain, limb pain, pain in the back.

Not known: myalgia, arthralgia.

Renal and urinary disorders:

Not known: Urinary hesitancy, micturition disorders.

Reproductive system and breast disorders:

Uncommon: decreased libido

Very rare: Priapism[8)].

General disorders and administration site conditions:

Common: Perspiration, hot flushes, oedema, influenza-like symptoms.

Not known: weakness, fatigue, fever.

Investigations:

Not known: Elevated liver enzymes

[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 with continued therapy

[4)] especially when associated with concomitant administration of other psychotropic drugs.

[5)] Clinical studies involving patients with pre – existing cardiac disease suggest that trazodone may be arrhythmogenic in some patient in this population. Arrhythmias identified include isolated premature ventricular contractions; ventricular couplets; short (3 – 4 beats) episodes of ventricular tachycardia.

[6)] Clinical studies in patients with pre-existing cardiac disease indicate that trazodone may be arrhythmogenic in some patients in that population

[7)] Adverse effects on hepatic function, sometimes severe, have been rarely reported. Should such effects occur trazodone should be immediately discontinued.

[8)] See also section 4.4.

General remarks:

Trazodone has no effect on arterial blood pCO_2 or pO_2 levels in patients with severe respiratory insufficiency due to chronic bronchial or pulmonary disease.

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 reporting system listed in Appendix V*.

4.9 Overdose

Symptoms:

The most frequently reported reaction to overdose have included drowsiness, dizziness, nausea and vomiting. In more serious cases coma, convulsions, hyponatraemia, hypotension, tachycardia, 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.

Overdose of trazodone in combination with other antidepressant drugs 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 redused. Cardiac monitoring is appropriate in symptomatic patients. .

Single brief convulsions do not require treatment. Control frequent or prolonged convulsions with intravenvenous 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

Pharmacotherapeutic group: Other antidepressants
ATC code: NO6AX05

Mechanisms of action
Trazodone is a sedative antidepressant with dual-serotonergic mechanism of action. Trazodone pre-synaptically inhibits serotonin re-uptake and post-synaptically blocks $5HT_{2A}$-receptors.

The sedative component of action is presumably based on the relatively highly pronounced antagonistic affinity for central α_1 receptors and a relatively poorly antagonistic affinity for H_1 receptors.

Besides the antidepressant and anxiolytic effect, trazodone has pro-sexual properties (promoting libido and erectile potency). The mechanism of action, however, is not yet known. Anti-α_1, anti-α_2 adrenergic and anti-serotonergic mechanisms in periphery and central nervous system are discussed.

Trazodone has no significant affinity for β-adrenergic, histaminergic H_2, dopaminergic and cholinergic receptors.

Trazodone demonstrated efficacy in various behaviour-pharmacological animal models used for testing antidepressant effects.

The active metabolite mCPP (m-chlorophenylpiperazine) is a non-specific serotonin-receptor agonist.

5.2 Pharmacokinetic properties

Absorption

Following oral administration trazodone hydrochloride is rapidly absorbed from the gastrointestinal tract, with T_{max} of 0.5 to 2 hours, and it is approximately 65 % bioavailable. When trazodone is taken with food, there may be a slight increase (up to 20%) in the total amount of drug absorbed (AUC), whereas the rate of absorption is delayed (C_{max} is lower and t_{max} is later). Administration after food minimises the risk of side effects. Steady state plasma levels are achieved after about four days of drug administration.

Distribution

Trazodone does not appear to selectively accumulate, although concentrations may be higher in liver, bone marrow, and brain. It is 85 % – 95 % plasma protein bound, with a volume of distribution (V_d) following a single oral 100 mg dose of 0.84 ± 0.16 L / Kg,

Biotransformation

Following absorption trazodone undergoes extensive hepatic metabolism by oxidation and hydroxylation to yield a range of metabolites. About 10 % is formed into m – chlorophenylpiperazine, which is an active metabolite. Other metabolites are the N – oxide derivative, diol derivative, hydroxy derivative, and conjugated compounds, all of which are inactive.

Human liver microsome studies *in vitro* have shown that cyctochrome P450 3A4 is responsible for metabolism to m – chlorophenylpiperazine, and cytochrome P450 2D6 is also involved in the metabolism.

Elimination

Trazodone is excreted mainly by the renal route (70%), mainly in the form of metabolites (only 0.15 % trazodone is excreted unchanged). Faecal excretion accounts for about 20 %. Trazodone is also excreted in breast milk.

The elimination is biphasic, with a half life around 1 hour for the initial phase, and about 8 hours for the second phase, giving a terminal elimination half life of 5 – 13 hours.

Renal patients

Trazodone is primarily eliminated via renal excretion in form of its inactive metabolites, and accumulation of the parent drug and active metabolite are therefore unlikely to occur in renal dysfunction. Dose adjustments may only be necessary in severe cases (see section 4.2 and 4.4). Dialysis does not significantly accelerate clearance of trazodone from the body.

5.3 Preclinical safety data

Acute toxicity studies were carried out in different species (dog, mouse, rat). Drowsiness, salivation, vomiting, dyspnoea, and convulsions were detected as symptoms of intoxication.
For intoxication in humans, see section 4.9.

No studies of the mutagenic potential are available.

Long-term studies on the carcinogenic potential of trazodone have only been performed in rats and showed no significant increase in neoplasms.

Embryotoxic effects (growth retardation, embryolethality) occurred in rats and rabbits after doses of 100-150 mg/kg BW/day.

No teratogenic effects were observed. Offspring of rats showed reduced birth weights after administration of 300 mg/kg BW/day in the peri-postnatal period. The fertility of male and female rats was not impaired by dosages up to 150 mg/kg BW/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Polyvidone K30 (E 1201)
Calcium hydrogen phosphate (E 341)
Microcrystalline cellulose (E 460i)
Sodium starch glycollate (E 468)
Magnesium stearate (E 470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Tablets are packed in PVC/aluminium blisters.
Pack sizes: 10, 20, 30, 60, 90, 100, 120, 180, 500, 1000 tablets

Not all listed pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz B.V.
Veluwezoom 22
1327 AH Almere
Nederland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 111061

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 24 maart 2014

Datum van laatste hernieuwing: 10 februari 2018

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 2 en 4.4: 11 mei 2020