Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zolpidem Tartrate Teva 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg zolpidem tartrate.
Excipient with known effect: each film-coated tablet contains 90.40 mg lactose monohydrate
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Zolpidem Tartrate Teva 10 mg film-coated tablets are white, oval, biconvex, film-coated tablets, scored on both sides and embossed with "ZIM 10" on one side.
Tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term treatment of insomnia in adults.
Benzodiazepines or benzodiazepine-like agents are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Posology
Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including the tapering off process, of four weeks. The tapering off process should be tailored to the individual.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status since the risk of abuse and dependence increases with the duration of treatment (see section 4.4).

The treatment should be taken in a single intake and not be re-administered during the same night.

Adults
The recommended daily dose for adults is 10 mg to be taken immediately at bedtime. The lowest effective daily dose of zolpidem should be used and must not exceed 10 mg.

Elderly
In elderly or debilitated patients who may be especially sensitive to the effects of zolpidem a dose of 5 mg is recommended. This dose should only be increased to 10 mg where the clinical response is inadequate and the drug is well tolerated. The total dose of zolpidem should not exceed 10 mg in any patient.

Hepatic impairment
Severe hepatic impairment
Zolpidem is contraindicated in patients with severe hepatic impairment as it may contribute to encephalopathy (see section 4.3).

Mild to moderate hepatic impairment
As clearance and metabolism of zolpidem tartrate is reduced in hepatic impairment a dose of 5 mg is recommended with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10mg only where the clinical response is inadequate and the drug is well tolerated. The total dose of zolpidem should not exceed 10 mg in any patient.

Paediatric population
Zolpidem Tartrate Teva is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in section 5.1.

Method of administration
Oral use.
The product should be taken with fluid.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Severe hepatic insufficiency.
Sleep apnoea syndrome.
Previously known complex sleep behaviours after taking zolpidem, see section 4.4.
Myasthenia gravis.
Acute and/or severe respiratory insufficiency.
Children and adolescents under 18 years of age.

4.4 Special warnings and precautions for use

General
The cause of insomnia should be identified wherever possible. The underlying factors should be treated before a hypnotic is prescribed. The failure of insomnia to remit after a 7-14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder, which should be evaluated.

General information relating to effects seen following administration of benzodiazepines or other hypnotic agents which should be taken into account by the prescribing physician are described below.

Tolerance
Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines and benzodiazapine-like agents may develop after repeated use for a few weeks.

Dependence
Use of benzodiazepines or benzodiazapine-like agents may lead to the development of abuse and/or physical and psychological dependence of these products. The risk of dependence increases with dose and duration of treatment and is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or drug abuse. These patients should be monitored carefully when receiving benzodiazepines or benzodiazepine-like agents.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations, delirium or epileptic seizures.

Rebound insomnia
A transient syndrome whereby the symptoms that led to treatment with a benzodiazepines or benzodiazapine-like agent recur in an enhanced form, may occur on withdrawal of hypnotic agent. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur when the medicinal product is being discontinued.

There are indications that, in the case of benzodiazepines and benzodiazapine-like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

As the risk of withdrawal symptoms/rebound phenomena are more likely to develop after abrupt discontinuation of treatment, it is recommended to decrease the dose gradually.

Somnambulism and associated behaviours

Sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, making phone calls or having sex, with amnesia of the event, have been reported in patients who had taken zolpidem and were not fully awake. These events may occur following the first or any subsequent use of zolpidem. The use of alcohol and other CNS-depressants with zolpidem appears to increase the risk of such behaviours, as does the use of zolpidem at doses exceeding the maximum recommended dose. Discontinuation of zolpidem should be strongly considered for patients who report such behaviours, due to the risk to the patient and others (see section 4.3).

Next-day psychomotor impairment
Like other sedative/hypnotic drugs, zolpidem has CNS-depressant effects.
The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:

- zolpidem is taken within less than 8 hours before performing activities that require mental alertness(see section 4.7);
- a dose higher than the recommended dose is taken;
- zolpidem is co-administered with other CNS depressants or with other drugs that increase the blood levels of zolpidem, or with alcohol or illicit drugs (see section 4.5).Zolpidem should be taken in a single intake immediately at bedtime and not be re-administered during the same night.

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2), but should not exceed 4 weeks including the tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration.

Amnesia

Benzodiazepines or benzodiazapine-like agents may induce anterograde amnesia. The condition usually occurs several hours after ingesting the product. In order to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 8 hours (see section 4.8).

Psychiatric and "paradoxical" reactions

When using benzodiazepines or benzodiazepine-like agents, reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, somnambulism, inappropriate behaviour, increased insomnia, delirium and other adverse behavioural effects are known to occur. Should this occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.

Risk from concomitant use of opioids

Concomitant use of zolpidem and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as zolpidem with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe zolpidem concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Severe Injuries

Due to its pharmacological properties, zolpidem can cause drowsiness and a decreased level of consciousness, which may lead

to falls and consequently to severe injuries, see also section 4.8.

Patients with Long QT syndrome

An *in vitro* cardiac electrophysiological study showed that under experimental conditions using very high concentration and pluripotent stem cells zolpidem may reduce the hERG related potassium currents. The potential consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of zolpidem treatment in patients with known congenital long QT syndrome should be carefully considered.

Specific patient groups

Elderly or debilitated patients

Should receive a lower dose: see recommended dosage (section 4.2).

Due to the myorelaxant effect there is a risk of falls and consequent injury particularly for elderly patients when they get up at night.

Renal insufficiency (see section 5.2)

Although dose adjustment is not necessary, caution should be exercised.

Chronic respiratory insufficiency

Caution should be observed when prescribing zolpidem since benzodiazepines have been shown to impair respiratory drive. It should also be taken into consideration that anxiety or agitation have been described as signs of decompensated respiratory insufficiency.

Hepatic insufficiency

Benzodiazepines and benzodiazapine-like agents are not indicated for the treatment of patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Mild to moderate hepatic impairment/insufficiency - See dose recommendations (see section 4.2, 4.3 and section 4.8).

Psychotic illness

Benzodiazepines and benzodiazapine-like agents are not recommended for the primary treatment.

Depression and suicidality

Some epidemiological studies suggest an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including zolpidem. However, a causal relationship has not been established.

Despite the fact that relevant clinical, pharmacokinetic and pharmacodynamic interactions with SSRI have not been demonstrated, zolpidem should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present. Due to the possibility of intentional overdose by the patient, the lowest amount of drug that is feasible should be supplied to these patients.

Benzodiazepines and benzodiazapine-like agents should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Pre-existing depression may be disclosed during use of zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

History of drug or alcohol abuse:

Benzodiazepines and benzodiazapine-like agents should be used with extreme caution in patients with a history of alcohol or drug abuse. These patients should be under careful surveillance when receiving zolpidem since they are at risk of habituation and psychological dependence.

Excipients

Zolpidem Tartrate Teva contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Zolpidem Tartrate Teva contains sodium, but less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol
Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

CNS depressants
Caution should be exercised when zolpidem is used in combination with other CNS depressants (see section 4.4). Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, muscle relaxants, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines (see section 4.8 and section 5.1). Therefore, concomitant use of zolpidem with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability (see section 4.4 and section 4.7). Also, isolated cases of visual hallucinations were reported in patients taking zolpidem with antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine.

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as zolpidem with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Co- administration of fluvoxamine may increase blood levels of zolpidem, concurrent use is not recommended.

In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

CYP450 inhibitors and inducers
Zolpidem is metabolised by some enzymes of the cytochrome P450-family in vitro.
The main enzyme is CYP3A4 with partial contribution of CYP1A2.

Rifampicin induces the metabolism of zolpidem, resulting in approximately 60% reduction in peak plasma concentrations and possibly decreased efficacy. Similar effects might be expected also with other strong inducers of cytochrome P450-enzymes like carbamazepine, phenytoin and St. John's Wort. Co-administration of St. John's Wort may decrease blood levels of zolpidem, concomitant use is not recommended.

Compounds that inhibit hepatic enzymes (particularly CYP3A4) may increase plasma concentrations and enhance the activity of zolpidem.

However, when zolpidem is administrated with itraconazole (CYP3A4 inhibitor), the pharmacokinetic and pharmacodynamic effects are not significantly different. The clinical relevance of these results is unknown.

Concomitant administration of zolpidem and ketoconazole, which is a potent CYP3A4 inhibitor, prolonged the half-life of zolpidem. The total exposure of zolpidem increased by 83 % and the apparent oral clearance was decreased. It is not necessary to perform a routine dose adjustment, but the patient should be informed about the potential increase in the sedative effect when ketoconazole and zolpidem are used concomitantly. Dose reduction of zolpidem may be considered when treatment with ketoconazole is introduced.

Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

Other drugs
When zolpidem was administered with warfarin, haloperidol, chlorpromazine, digoxin or ranitidine, no significant pharmacokinetic interactions were observed

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspect that she is pregnant.

Pregnancy
There are no or limited amount of data from the use of zolpidem in pregnant women.

Zolpidem crosses the placenta.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

For benzodiazepines or benzodiazepine-like substances a large amount of data on pregnant women (more than 1000 pregnancy outcomes) collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines or benzodiazepine-like substances during the first trimester of pregnancy. However, certain case-control studies reported an increased incidence of cleft lip and palate associated with use of benzodiazepines during pregnancy.

Cases of reduced foetal movement and foetal heart rate variability have been described after administration of benzodiazepines or benzodiazepine-like substances during the second and/or third trimester of pregnancy. Administration of zolpidem during the late phase of pregnancy or during labour has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties ('floppy infant syndrome'), and respiratory depression, due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.

Infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the latter stages of pregnancy may develop withdrawal symptoms in the postnatal period as a result of physical dependence. Appropriate monitoring of the newborn in the postnatal period is recommended.

Zolpidem should not be used during pregnancy, especially in the first trimester.

Breastfeeding
Zolpidem passes into breast milk in minimal amounts. Zolpidem should therefore not be used during breast-feeding since effects on the infant are not studied.

Fertility
There are no data on fertility for zolpidem.

4.7 Effects on ability to drive and use machines

Zolpidem has major influence on the ability to drive and use machines.
Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision and reduced alertness and impaired driving the morning after therapy (see section 4.8). In order to minimise this risk a resting period of at least 8 hours is recommended between taking zolpidem and driving, using machinery and working at heights.
Driving ability impairment and behaviours such as 'sleep-driving' have occurred with zolpidem alone at therapeutic doses. Furthermore, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such behaviours (see section 4.4 and 4.5). Patients should be warned not to use alcohol or other psychoactive substances when taking zolpidem.

4.8 Undesirable effects

Daytime sleepiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia and double vision are all side effects that occur primarily at the start of treatment and usually disappear again with repeated use. Other side effects, such as gastrointestinal complaints, changes in libido and skin reactions, are reported as well.

There are indications that the occurrence of side effects that have been linked to the use of zolpidem is dose dependent; this applies particularly to some side effects experienced in relation to the central nervous system.

The following frequency data is the basis for the evaluation of undesirable effects:

Very common (³ 1/10)
Common (³ 1/100 to < 1/10)
Uncommon (³ 1/1,000 to < 1/100)
Rare (³ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
not known (cannot be estimated from the available data)

There is evidence of a dose-relationship for adverse effects associated with zolpidem tartrate use, particularly for certain CNS and gastrointestinal events.

These undesirable effects occur most frequently in elderly patients.
These effects seem to be related with individual sensitivity and to appear more often within the hour following the drug intake if the patient does not go to bed or does not sleep immediately (see section 4.2).

Infections and infestations
Common: upper respiratory tract infection, lower respiratory tract infection

Immune system disorders
Not known: angioneurotic oedema

Metabolism and nutrition disorders
Uncommon: appetite disorder

Psychiatric disorders
Common: hallucination[3], agitation[3], nightmare[3], depression[2] (see section 4.4)
Uncommon: confusional state, irritability, restlessness, aggression, somnambulism (see section 4.4), euphoric mood, parasomnia (see section 4.4)
Rare: libido disorder
Very rare: delusion, dependence[4]
Not known: abuse[4], paradoxical drug reactions[3], abnormal behaviour[3], psychosis[3], delirium (see section 4.4)

Nervous system disorders
Common: somnolence, drowsiness during the following day, numbed emotions, reduced alertness, headache, dizziness, ataxia, exacerbated insomnia, cognitive disorder[1], amnesia[1]
Uncommon: paraesthesia, tremor, disturbance in attention, speech disorder
Not known: depressed level of consciousness

Eye disorders
Uncommon: diplopia, vision blurred
Very rare: visual impairment

Ear and labyrinth disorders
Common: vertigo

Respiratory, thoracic and mediastinal disorders
Very rare: respiratory depression (see section 4.4)

Gastrointestinal disorders
Common: diarrhoea, nausea, vomiting, abdominal pain

Hepatobiliary disorder
Uncommon: liver enzymes elevated
Rare: hepatocellular, cholestatic or mixed liver injury (see section 4.2, section 4.3 and section 4.5)

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, hyperhidrosis
Rare: urticaria

Musculoskeletal and connective tissue disorders
Common: back pain
Uncommon: arthralgia, myalgia, muscle spasms, neck pain, muscular weakness

General disorders and administration site conditions
Common: fatigue
Rare: gait disturbance
Not known: drug tolerance, fall (predominantly in elderly patients and when zolpidem tartrate was not taken in accordance with prescribing recommendation)

[1]*Amnesia*
Anterograde amnesia may occur with therapeutic doses; the risk of which increases with higher doses. Amnesia may be associated with inappropriate behaviour (see section 4.4).

[2]*Depression*
Pre-existing depression may be unmasked with the use of benzodiazepines or benzodiazepine-like substances (see section 4.4).

[3]*Psychiatric and 'paradoxical' reactions*
Reactions such as restlessness, agitation, irritability, aggression, delusion, anger, nightmare, hallucinations, psychoses, abnormal behaviour and other behavioural disorders may occur when using benzodiazepines or benzodiazepine-like substances. In rare cases, these reactions can be quite serious. The chance of these reactions is greater in elderly.

[4]*Dependence*
Use (even in therapeutic doses) may result in physical dependence: stopping treatment can result in withdrawal or 'rebound' symptoms (see section 4.4). Psychological dependence is possible too. Abuse has been reported in drug addicts who are addicted to various drugs.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
In cases of overdose involving zolpidem alone or with other CNS-depressant agents (including alcohol), impairment of consciousness up to coma, and more severe symptomatology, including fatal outcomes have been reported.

Individuals have fully recovered from overdoses up to 400 mg of zolpidem, 40 times the recommended dose.

Management

General symptomatic and supportive measures should be used. Immediate gastric lavage should be used where appropriate. Intravenous fluids should be administered as needed. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Monitoring of respiratory and cardiovascular functions should be considered. Sedating drugs should be withheld even if excitation occurs.

Use of flumazenil may be considered when serious symptoms are observed.
Flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). In the treatment of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Due to the high distribution volume and protein binding of zolpidem, haemodialysis and forced diuresis are not effective measures. Hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine related drugs
ATC code: NO5CFO2

Zolpidem, an imidazopyridine is a benzodiazepine-like hypnotic agent. In experimental studies it was shown that it has sedative effects at lower dosages than those required to exert anticonvulsant, myorelaxant or anxiolytic effects. These effects are related to a specific agonist action at central receptors belonging to the "GABA-omega" (BZ1 & BZ2) macromolecular receptor" complex, modulating the opening of the chloride ion channel. Zolpidem acts primarily upon omega (BZ1) receptor subtypes. The clinical relevance of this is not known.

The randomized trials only showed convincing evidence of efficacy of 10 mg zolpidem.
In a randomized double-blind trial in 462 non-elderly healthy volunteers with transient insomnia, zolpidem 10 mg decreased the mean time to fall asleep by 10 minutes compared to placebo, while for 5 mg zolpidem this was 3 minutes.
In a randomized double-blind trial in 114 non-elderly patients with chronic insomnia, zolpidem 10 mg decreased the mean time to fall asleep by 30 minutes compared to placebo, while for 5 mg zolpidem this was 15 minutes.
In some patients, a lower dose of 5 mg could be effective.

Paediatric population
Safety and efficacy of zolpidem have not been established in children aged less than 18 years. A randomized placebo-controlled study in 201 children aged 6-17 years with insomnia associated with Attention Deficit Hyperactivity Disorder (ADHD) failed to demonstrate efficacy of zolpidem 0.25 mg/kg/day (with a maximum of 10 mg/day) as compared to placebo. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5 % versus 1.5 %), headache (12.5 % versus 9.2 %), and hallucinations (7.4 % versus 0 %) (see sections 4.2).

5.2 Pharmacokinetic properties

Absorption
Zolpidem has both a rapid absorption and onset of hypnotic effect. Bioavailability is 70% following oral administration. It demonstrates linear kinetics in the therapeutic dose range. The therapeutic plasma level is between 80 and 200 ng/ml. Peak plasma concentration is reached at between 0.5 and 3 hours after administration.
Interindividual variability is high, (CV% of AUC is 60-70 % and for Cmax 40-50 %).

Distribution
The distribution volume in adults is 0.54 L/kg and decreases to 0.34 L/kg in the elderly.

Protein binding amounts to 92%. First pass metabolism by the liver amounts to approximately 35%. Repeated administration has been shown not to modify protein binding indicating a lack of competition between zolpidem and its metabolites for binding sites.

Elimination
The elimination half-life is short, with a mean of 2.4 hours and a duration of action up to 6 hours.

All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%).

Zolpidem has been shown in trials to be non-dialysable.

Clearance is approximately 300 ml/min.

Special populations
In patients with renal insufficiency, a moderate reduction in clearance is observed (independent of possible dialysis). The other pharmacokinetic parameters remain unaffected.

In elderly patients the bio-availability of zolpidem is increased.
Reduced clearance, approximately 100 ml/min, has been observed in elderly. The maximal plasma concentration is increased by approximately 80 % without a significant increase of the half life (around 3 hours) in a patient group aged 81-95 years.

In patients with hepatic impairment the bioavailability of zolpidem is increased by 80 % and the half-life is increased from 2.4 hours in healthy individuals to 9.9 hours in patients with hepatic impairment.

In patients with liver cirrhosis a 5-fold increase in AUC and a 3-fold increase in half-life was observed.

5.3 Preclinical safety data

Preclinical effects were only observed at dosages well above the maximum human exposure levels and are therefore of little significance for clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose (E460)
Sodium starch glycolate Type A
Hypromellose (E464)
Magnesium stearate (E572)

Coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

7, 10, 14, 15, 20, 28, 30, 50xl, 90, 100 film-coated tablets packed in PVC/PE/PVDC-Al or PVC/PVDC-Al blisters.
Not all pack sizes may be marketed.

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.

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/095/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th February 2010
Date of last renewal: 2nd March 2014

10 DATE OF REVISION OF THE TEXT

November 2023