SCHEDULING STATUS:

S5

PROPRIETARY NAME AND DOSAGE FORM:

STILNOX tablets

COMPOSITION:

Each tablet contains 10 mg of zolpidem tartrate.

Excipients: Hypromellose (6 m.pas), lactose monohydrate, macrogol 400, magnesium stearate, microcrystalline cellulose (Avicel PH101), sodium starch glycolate (type A) and titanium dioxide suspension (CI 778891).

Contains sugar (90,40 mg lactose monohydrate per tablet).

CATEGORY AND CLASS:

A 2.2. Sedatives, hypnotics.

PHARMACOLOGICAL ACTION:

Zolpidem is an imidazopyridine compound with sedative/hypnotic effects. These effects are related to a specific agonist action at central receptors belonging to GABA-omega benzodiazepine-1 and benzodiazepine-2 macromolecular receptor complex, modulating

the opening of the chloride ion channel. Zolpidem acts primarily upon the omega-1 (benzodiazepine-1) receptor subtypes. The clinical relevance of this is not known.

Pharmacokinetics:

Absorption:

After oral administration, the bioavailability of zolpidem is about 70 %, reaching peak plasma concentration between 0,5 and 3 hours after dosing.

Distribution:

At therapeutic dose levels, the pharmacokinetics are linear. The degree of plasma protein binding is about 92 %. The plasma elimination half-life is about 2,5 hours (1,4 - 3,8 hours). The distribution volume in adults is 0,54 ± 0,02 l/kg. The distribution volume decreases to 0,34 ± 0,05 l/kg in the very elderly.

Excretion:

Zolpidem is excreted in the form of inactive metabolites (hepatic metabolism), mainly in the urine (56 %) and faeces (37 %). It has no inducing effects on hepatic enzymes. In elderly subjects, clearance is reduced. The peak concentration is increased by about 50 % and elimination half-life by 32 %.

In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.

Bioavailability:

In patients with hepatic insufficiency, the bioavailability of zolpidem is increased. Clearance is reduced and the elimination half-life prolonged (about 10 hours).

INDICATIONS:

STILNOX is indicated for the short term treatment of insomnia.

STILNOX or a short acting hypnotic, is only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

CONTRAINDICATIONS:

- A hypersensitivity to zolpidem or any of the inactive ingredients.
- Myasthenia gravis.
- Sleep apnoea syndrome.
- Acute and/or severe respiratory insufficiency.
- Severe hepatic insufficiency (see WARNINGS).
- Paediatric population under the age of 18.
- Safety in pregnancy and lactation has not been established (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS:

The cause of insomnia should be identified wherever possible and the underlying factors treated before STILNOX is prescribed. The failure of insomnia to remit after a 7 -

14 days course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re-evaluated at regular intervals.

Respiratory Insufficiency:

Caution should be observed when prescribing STILNOX to patients with chronic respiratory insufficiency as respiratory drive may be suppressed.

Severe Hepatic Insufficiency:

STILNOX is contraindicated in patients with severe hepatic insufficiency as it may precipitate encephalopathy (see CONTRAINDICATIONS).

Risks from concomitant use with opioids:

Concomitant use of benzodiazepines and other sedative-hypnotic medicines, including STILNOX, may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe STILNOX concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation.

Paediatric patients:

STILNOX is contraindicated in patients under the age of 18 years due to increased occurrence of adverse effects including dizziness, headache and hallucinations.

Elderly:

See dose recommendations.

Psychotic illness:

STILNOX should not be used as the primary treatment of psychotic illness.

Amnesia:

STILNOX may induce anterograde amnesia. The condition occurs most often several hours after ingesting STILNOX and therefore, to reduce this risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours (see Side Effects).

Suicidality and depression:

Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including STILNOX. A causal relationship has not been established.

STILNOX should not be used as the primary treatment of depressive syndromes. STILNOX should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present, therefore, the least amount of

STILNOX that is feasible, should be supplied to these patients because of the possibility of intentional overdosage by the patient.

Pre-existing depression may be unmasked during use of STILNOX.

Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Other psychiatric and "paradoxical" reactions:

Other psychiatric and paradoxical reactions like restlessness, exacerbated insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, abnormal behaviour and other adverse behavioural effects are known to occur when using STILNOX. Should this occur, use of STILNOX should be discontinued. These reactions are more likely to occur in the elderly. See Side Effects.

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 from the event, have been reported in patients who had taken STILNOX and were not fully awake. The use of alcohol and other CNS-depressants with STILNOX appears to increase the risk of such behaviours, as does the use of STILNOX at doses exceeding the maximum recommended dose. Discontinuation of STILNOX should strongly be considered for patients who report such behaviours.

Psychomotor impairment:

The risk of psychomotor impairment, including impaired driving ability, is increased if: STILNOX is taken within less than 7 – 8 hours before performing activities that require mental alertness, a dose higher than the recommended dose is taken, or STILNOX is co-administered with other CNS depressants, alcohol, or with other medicines that increase the blood levels of STILNOX.

Duration of treatment:

The duration of treatment should be as short as possible and should not exceed 4 weeks, including the tapering off process. Extensions 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, and to explain precisely how the dosage will be progressively decreased.

Tolerance:

Some loss of efficacy of the hypnotic effects of STILNOX may develop after repeated use for a few weeks.

Rebound insomnia:

A transient syndrome, whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form, may occur on withdrawal of

STILNOX treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

The syndrome is more likely to develop if STILNOX is discontinued abruptly, and therefore treatment with STILNOX should be withdrawn gradually.

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

In the case of hypnotics with a short duration of action, such as STILNOX, withdrawal phenomena can become manifest within the dosage interval.

Dependence and abuse:

Use of STILNOX may lead to the development of physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. Patients with a history of psychiatric disorders should be under careful surveillance when receiving STILNOX. Patients with a history of alcohol or drug abuse – see History of alcohol and drug abuse.

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 or epileptic seizures.

Sedatives/hypnotics including STILNOX have produced withdrawal signs and symptoms following abrupt discontinuation. These symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. The following adverse events have been reported fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness and abdominal discomfort.

These reported adverse events occurred at an incidence of 1 % or less. However, available data cannot provide a reliable estimate of the incidence of dependence during treatment at recommended doses. Post-marketing reports of abuse, dependence and withdrawal have been received.

Patients with a history of psychiatric disorders or addiction to, or abuse of, drugs or alcohol are at increased risk of habituation and dependence. Patients with a history of psychiatric disorders should be under careful surveillance when receiving STILNOX or any other hypnotic. Patients with a history of addiction to, or abuse of, drugs or alcohol – see History of alcohol and drug abuse.

History of alcohol and drug abuse:

STILNOX should not be used in patients with a history of alcohol or drug abuse.

Severe injuries:

Due to its pharmacological properties, STILNOX can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

Patients with Long QT syndrome:

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

Effects on ability to drive or to use machines:

Vehicle drivers and machine operators should be warned that there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness and vertigo, sleepiness, blurred/double vision, reduced alertness and impaired driving the morning after therapy.

If insufficient sleep duration occurs, the likelihood of impaired alertness may increase. In order to minimise this risk a full night of sleep (7 – 8 hours) is recommended.

Furthermore, the co-administration of STILNOX with alcohol and other CNS depressants increases the risk of such effects. Patients should be warned not to use alcohol or other psychoactive substances when taking STILNOX.

Lactose intolerance:

Since STILNOX tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption, should not take STILNOX.

INTERACTIONS:

Alcohol:

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

CNS depressants:

Enhancement of the central depressive effects may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic medicines, anaesthetics and sedative

antihistamines. Concomitant use of STILNOX with these medicines may increase drowsiness and psychomotor impairment, including impaired driving ability.

Co-administration of fluvoxamine may increase blood levels of STILNOX; concurrent use is not recommended (see INTERACTIONS: CYP450 inhibitors and inducers).

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

Opioids:

The concomitant use of benzodiazepines and other sedative-hypnotic medicines, including STILNOX, and 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 WARNINGS AND SPECIAL PRECAUTIONS).

CYP450 inhibitors and inducers:

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of some hypnotics like STILNOX.

STILNOX is metabolised via several hepatic cytochrome P450 enzymes: the main enzyme being CYP3A4 with the contribution of CYP1A2.

The pharmacodynamic effect of STILNOX is decreased when it is administered with a CYP3A4 inducer such as rifampicin and St John's Wort. Co-administration of St. John's Wort may decrease blood levels of STILNOX, concurrent use is not recommended.

However, when STILNOX was administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

Co-administration of STILNOX with ketoconazole (200 mg twice daily), a potent CYP3A4 inhibitor, prolonged STILNOX elimination half-life, increased total AUC, and decreased apparent total clearance when compared to STILNOX plus placebo. The total AUC for STILNOX, when co-administered with ketoconazole, increased by a factor of 1,83 when compared to STILNOX alone. A routine dosage adjustment is not considered necessary, but patients should be advised that use of STILNOX with ketoconazole may enhance the sedative effects.

Fluvoxamine is a strong inhibitor of CYP1A2 and a moderate to weak inhibitor of CYP2C9 and CYP3A4. Co-administration of fluvoxamine may increase blood levels of STILNOX, concurrent use is not recommended.

Ciprofloxacin has been shown to be a moderate inhibitor of CYP1A2 and CYP3A4. Co-administration of ciprofloxacin may increase blood levels of STILNOX, concurrent use is not recommended.

Other medicines:

When STILNOX was administered with warfarin, digoxin, ranitidine or cimetidine, no significant pharmacokinetic interactions were observed.

HUMAN REPRODUCTION:

Safety in pregnancy and lactation has not been demonstrated (see CONTRAINDICATIONS).

The use of STILNOX in pregnancy and breastfeeding should be avoided.

Pregnancy:

If STILNOX is administered during the late phase of pregnancy, or during labour, effects on the neonate such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product.

Infants born to mothers who take STILNOX chronically during the latter stages of pregnancy may develop physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period.

Lactation:

Small quantities of zolpidem appear in breast milk. The use of STILNOX in breastfeeding mothers is, therefore not recommended (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

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.

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.

STILNOX should be taken immediately before going to bed, or in bed.

STILNOX should be taken in a single intake and not be readministered during the same night.

Dose:

The recommended daily dose for adults is 10 mg immediately before bedtime, or in bed. The lowest effective daily dose of STILNOX should be used and must not exceed 10 mg.

Elderly:

Since elderly or debilitated patients may be especially sensitive to the effects of STILNOX, in these patients, a dose of 5 mg is recommended. The total STILNOX dose should not exceed 10 mg in this population.

Children:

Safety and effectiveness of STILNOX in paediatric patients under the age of 18 years have not been established. STILNOX should not be prescribed in this population. (see CONTRAINDICATIONS).

Hepatic impairment:

In patients with hepatic insufficiency, the recommended starting dose is 5 mg and particular caution must be exercised in elderly patients.

SIDE EFFECTS:

The following CIOMS frequency rating is used, when applicable:

Very common: ≥ 10 %; Common: ≥ 1 % and < 10 %; Uncommon: ≥ 0,1 % and < 1 %; Rare: ≥ 0,01 % and < 0,1 %; Very rare: < 0,01 %.

Not known: Cannot be estimated based on available data.

There is evidence of a dose-relationship for adverse effects associated with STILNOX use, particularly for certain CNS events. They occur most frequently in elderly patients.

Infections and infestations:

Common: upper respiratory tract infection, lower respiratory tract infection

Nervous system disorders:

Common: somnolence, headache, dizziness, exacerbated insomnia, cognitive disorders such as anterograde amnesia (amnestic effects may be associated with inappropriate behaviour)

Uncommon: paraesthesia, tremor

Depressed level of consciousness, disturbance in attention and speech disorder have been reported but the frequency is not known.

Psychiatric disorders:

Common: hallucinations, agitation, nightmare

Uncommon: confusional state, irritability

Restlessness, aggression, delusion, anger, abnormal behaviour, somnambulism (see WARNINGS AND SPECIAL PRECAUTIONS: somnambulism and associated behaviours"), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), libido disorder, depression, euphoric mood have been reported but the frequencies are not known.

Most of these psychiatric side effects are related to paradoxical reactions.

General disorders and administrative site conditions:

Common: fatigue

Gait disturbances, drug tolerance and fall have been reported but the frequencies are not known.

Eye disorders:

Uncommon: diplopia, blurred vision

Rare: visual impairment

Respiratory, thoracic and mediastinal disorders:

Not known: respiratory depression

Gastrointestinal disorders:

Common: diarrhoea, nausea, vomiting, abdominal pain

Metabolism and nutrition disorders:

Uncommon: appetite disorder

Musculoskeletal and connective tissue disorders:

Common: back pain

Uncommon: arthralgia, myalgia, muscle spasms, neck pain

Muscular weakness has been reported but the frequency is not known.

Skin and subcutaneous tissue disorders:

Rash, angioneurotic oedema, pruritus, urticaria and hyperhidrosis have been reported but the frequencies are not known.

Hepatobiliary disorders:

Elevated liver enzymes, hepatocellular, cholestatic or mixed liver injury have been reported but the frequency is not known.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Signs and symptoms

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

Management:

General symptomatic and supportive measures should be used. Sedating medicines should be withheld even if excitation occurs.

The use of benzodiazepine-antagonists (e.g. flumazenil) may be considered where serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

STILNOX is not dialysable.

IDENTIFICATION:

White to off-white film-coated oblong tablet, scored, engraved (“STILNOX” on one side).

PRESENTATION:

30 tablets in clear PVC and aluminium foil blister packs.

STORAGE INSTRUCTIONS:

Do not store above 30 °C. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

29/2.2/0651

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION:

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