Professional information for IVEDAL

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

IVEDAL, 10 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of zolpidem tartrate.

Excipients with known effects:

Contains sugar (90,4 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White to off-white, film-coated, oblong tablet, scored, and engraved “SN 10” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IVEDAL is indicated for the short-term treatment of insomnia in adults.

IVEDAL, or a short-acting hypnotic, is 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.
In certain cases, extension beyond the maximum treatment period may be necessary; if so, extension beyond the maximum treatment period 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).
IVEDAL should be taken immediately before going to bed, or in bed.
IVEDAL should be taken in a single intake and not be re-administered 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 IVEDAL should be used and must not exceed 10 mg.

Special populations

Elderly patients:

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

Children:

Safety and effectiveness of IVEDAL in paediatric patients under the age of 18 years have not been established. IVEDAL should not be prescribed in this population (see section 4.3). The available evidence from placebo-controlled clinical trials is presented in section 5.1.

Hepatic impairment:

As clearance and metabolism of zolpidem tartrate, as in IVEDAL, is reduced in hepatic impairment; dosage should begin at 5 mg in these patients with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg only where the clinical response is inadequate, and the medicine is well tolerated.
IVEDAL must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy (see section 4.3).

Method of administration

Oral administration.

4.3 Contraindications

- Hypersensitivity to zolpidem tartrate or any of the excipients listed in section 6.1.
- Myasthenia gravis.
- Sleep apnoea syndrome.
- Acute and/or severe respiratory insufficiency.
- Severe hepatic insufficiency (see section 4.4).
- Paediatric population under the age of 18.
- Safety in pregnancy and lactation has not been established (see section 4.6).
- Known to have previously experienced complex sleep behaviours after taking IVEDAL (see section 4.4).

4.4 Special warnings and precautions for use

The cause of insomnia should be identified wherever possible and the underlying factors treated before IVEDAL 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 IVEDAL to patients with chronic respiratory insufficiency as respiratory drive may be suppressed.

Severe hepatic insufficiency:

IVEDAL is contraindicated in patients with severe hepatic insufficiency as it may precipitate encephalopathy (see section 4.2 and section 4.3).

Risks from concomitant use with opioids:

Concomitant use of opioids with benzodiazepines or other sedative-hypnotic medicines, including IVEDAL, 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 IVEDAL 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. In this respect, it is strongly recommended to inform patients to be aware of these symptoms (see section 4.5).

Paediatric patients:

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

Elderly patients:

See section 4.2 for dose recommendations.

Psychotic illness:

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

Amnesia:

IVEDAL may induce anterograde amnesia. The condition occurs most often several hours after ingesting IVEDAL and therefore, to reduce this risk, patients should ensure that they will be able to have uninterrupted sleep of 7 to 8 hours (see section 4.8).

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 IVEDAL. A causal relationship has not been established. IVEDAL should not be used as the primary treatment of depressive syndromes. IVEDAL should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present, therefore, the least amount of IVEDAL 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 IVEDAL.

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, delirium and other adverse behavioural effects are known to occur when using IVEDAL. Should this occur, use of IVEDAL should be discontinued. These reactions are more likely to occur in elderly patients (see section 4.8).

Somnambulism and associated behaviours:

Complex sleep behaviours, including 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 IVEDAL and were not fully awake. Patients can be seriously injured or injure others during complex sleep behaviours. Such injuries may result in a fatal outcome.

Post-marketing reports have shown that complex sleep behaviours may occur with IVEDAL alone at recommended doses, with or without the concomitant use of alcohol or other central nervous system (CNS) depressants.

Discontinue treatment immediately if a patient experiences complex sleep behaviour.

Next-day psychomotor impairment:

IVEDAL has CNS-depressant effects. The risk of psychomotor impairment, including impaired driving ability, is increased if: IVEDAL 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 IVEDAL is co-administered with other CNS depressants, alcohol, or with other medicines that increase the blood levels of IVEDAL (see section 4.5 and section 4.7).

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 IVEDAL 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 IVEDAL treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.
The syndrome is more likely to develop if IVEDAL is discontinued abruptly, and therefore treatment with IVEDAL 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 IVEDAL is being discontinued.
In the case of hypnotics with a short duration of action, such as IVEDAL, withdrawal phenomena can become manifest within the dosage interval.

Dependence and abuse:

Use of IVEDAL may lead to the development of abuse and/or physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment. The risk of abuse and dependence is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or medicine abuse. IVEDAL should be used with extreme caution in patients with current or a history of alcohol, substance or medicine abuse or dependence. 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, 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.

Sedatives/hypnotics including IVEDAL 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, light-headedness, 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.

History of alcohol and drug abuse:

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

Severe injuries:

Due to its pharmacological properties, IVEDAL 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 IVEDAL 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 IVEDAL treatment in patients with known congenital long QT syndrome should be carefully considered.

Lactose intolerance:

Since IVEDAL tablets contain lactose monohydrate, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take IVEDAL.

4.5 Interaction with other medicines and other forms of interaction

Alcohol:

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when IVEDAL 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 IVEDAL with these medicines may increase drowsiness and psychomotor impairment, including impaired driving ability.

Co-administration of fluvoxamine may increase blood levels of IVEDAL; concurrent use is not recommended (see 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 IVEDAL, 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 section 4.4).

CYP450 inhibitors and inducers:

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

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

The pharmacodynamic effect of IVEDAL 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 IVEDAL; concurrent use is not recommended.

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

Other medicines:

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

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been demonstrated (see section 4.3).

Pregnancy:

The use of IVEDAL is not recommended during pregnancy.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Zolpidem crosses the placenta.

A large amount of data on pregnant women (more than 1 000 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 fetal movement and fetal 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 IVEDAL 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 IVEDAL.
Cases of severe neonatal respiratory depression have been reported.

Infants born to mothers who took IVEDAL chronically during the latter stages of pregnancy may have developed physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

If IVEDAL is prescribed to a woman of childbearing potential, she should be warned to contact her doctor about stopping the product if she intends to become or suspects that she is pregnant.

Lactation:

Small quantities of zolpidem appear in breast milk. The use of IVEDAL in breastfeeding mothers is therefore not recommended (see section 4.3).

4.7 Effects on ability to drive and use machines

IVEDAL has major influence on the ability to drive and 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 (see section 4.8).

In order to minimise this risk a resting period of at least 8 hours is recommended between taking IVEDAL and driving, using machinery and working at heights.

Driving ability impairment and behaviours such as "sleep-driving" have occurred with IVEDAL alone at therapeutic doses.

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

4.8 Undesirable 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-response relationship for adverse effects associated with IVEDAL 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

Immune system disorders:

Not known: angioneurotic oedema

Metabolism and nutrition disorders:

Uncommon: appetite disorder

Psychiatric disorders:

Common: hallucinations, agitation, nightmare, depression (see section 4.4)

Uncommon: confusional state, irritability, restlessness, aggression, somnambulism (see section 4.4), euphoric mood

Rare: libido disorder

Very rare: delusion, dependence (withdrawal symptoms or rebound effects may occur after treatment discontinuation)

Not known: anger, abnormal behaviour, complex sleep behaviours (see section 4.4), delirium.

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

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, disturbance in attention and speech disorder

Rare: depressed level of consciousness

Eye disorders:

Uncommon: diplopia, blurred vision

Rare: visual impairment

Respiratory, thoracic and mediastinal disorders:

Very rare: respiratory depression (see section 4.4)

Gastrointestinal disorders:

Common: diarrhoea, nausea, vomiting, abdominal pain

Hepato-biliary disorders:

Uncommon: elevated liver enzymes

Rare: hepatocellular, cholestatic or mixed liver injury (see sections 4.2, 4.3 and 4.4)

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 disturbances, fall (predominantly in elderly patients and when IVEDAL was not taken in accordance with prescribing recommendation) (see section 4.4)

Not known: drug tolerance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of IVEDAL is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the "Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.
Side effects can be reported directly to Sanofi's Pharmacovigilance Unit at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

Signs and symptoms:

In cases of overdose involving IVEDAL 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.

Flumazenil is reported to have an elimination half-life of about 40 – 80 minutes. Patients should be kept under close observation because of this short duration of action; further doses of flumazenil may be necessary.

However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

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

IVEDAL is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.2. Sedatives, hypnotics.

Pharmacotherapeutic groups: Nervous system, Psycholeptics, Hypnotics and sedatives, Benzodiazepine related drugs.

ATC code: N05CF02.

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.

Paediatric population

Safety and efficacy of zolpidem tartrate have not been established in children aged less than 18 years. A randomised 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 tartrate 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 tartrate 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 and 4.3).

5.2 Pharmacokinetic properties

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).

5.3 Preclinical safety data

No data of therapeutic relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Hypromellose (6 mPa.s)

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose (Avicel PH101)

Sodium starch glycolate (type A)

Film coating:

Hypromellose (6 mPa.s)

Macrogol 400

Titanium dioxide suspension (E171, CI 778891).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Protect from light and moisture.

6.5 Nature and contents of container

14, 28 or 30 tablets in clear PVC and aluminium foil blister strips.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand 1685

South Africa

8. REGISTRATION NUMBER

37/2.2/0540

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 07 May 2004

10. DATE OF REVISION OF THE TEXT

24 January 2021