

ستیلنوکس • اسٹیلنوکس

(زولپیدیم) (منقسم گولیاں)

10 mg

sanofi aventis

Zolpidem tartrate 10 mg film-coated scored tablet

COMPOSITION

Each scored film-coated tablet contains:

Zolpidem tartrate 10mg

PHARMACEUTICAL FORM

Scored film-coated tablets

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Zolpidem is an imidazopyridine hypnotic agent related to the benzodiazepines. Experimental studies have shown that it has sedative activity at doses lower than those required to obtain anticonvulsive, muscle relaxant or anxiolytic activity.

These effects can be explained by selective agonist activity on the GABA- ω (BZ1 and BZ2) macromolecular receptor complex, which modulates opening of the chlorine channel. Zolpidem preferentially binds to ω 1 receptors (BZ1). In man, zolpidem decreases sleep latency, decreases the number of nocturnal awakenings, increases total sleep duration and improves sleep quality. These effects are associated with a characteristic electroencephalographic profile, which differs from that of the benzodiazepines. Nighttime sleep laboratory studies have showed that zolpidem prolongs both stage II and deep sleep (stages III and IV). At the recommended dosage, zolpidem does not affect the total duration of REM sleep.

Pharmacokinetic properties

Absorption

After oral administration, the bioavailability of zolpidem is approximately 70%. Maximum plasma concentrations are reached in 0.5 to 3 hours.

Distribution

At therapeutic doses, zolpidem displays linear pharmacokinetics. Plasma protein binding is approximately 92%. The distribution volume in adults is $0.54 + 0.02$ l/kg.

Elimination

Zolpidem is metabolised in the liver and excreted as inactive metabolites mainly in the urine (approximately 60%) and feces (approximately 40%). It does not induce hepatic enzymes. The mean plasma half-life is 2.4 hours (range: 0.7 to 3.5 hours).

In elderly subjects, hepatic clearance is reduced and the plasma peak is increased by approximately 50%, without significant prolongation of the half-life (average 3 hours). The distribution volume is decreased to $0.34 + 0.05$ l/kg.

In patients with renal insufficiency, whether on dialysis or not, there is a moderate decrease in renal clearance. Other kinetic parameters are not modified. Zolpidem cannot be dialysed. In patients with hepatic insufficiency, zolpidem bioavailability is increased, its clearance somewhat reduced and elimination half-life increased (approximately 10 hours).

THERAPEUTIC INDICATIONS

- Occasional insomnia
- Transient insomnia
- Chronic insomnia

DOSAGE AND METHOD OF ADMINISTRATION

Oral route.

In all cases, the dosage should be taken just before bedtime.

Dosage

Adults below the age of 65 years: one 10 mg tablet per day.

Adults over the age of 65 years or subjects with hepatic insufficiency: the recommended dosage is 1/2 tablet per day and should only be increased to 1 tablet in very rare cases.

In all cases, the dosage should not exceed one 10 mg tablet per day. In the absence of relevant data, the use of STILNOX, is not recommended in children.

Method of administration

Treatment duration

Treatment should be as brief as possible, from a few days to a maximum of four weeks.

- For occasional insomnia (due to travel for example), the treatment duration should not exceed two to five days.

- For transient insomnia (associated with a serious event, for example), the treatment duration should not exceed two to three weeks.

In some cases it may be necessary to continue the treatment for more than four weeks; this should only be undertaken after a careful reevaluation of the patient.

Mode of treatment discontinuation

For very brief treatments, reduction of the dosage is not necessary.

For prolonged treatment or when doses are above those recommended, a gradual treatment discontinuation allows to minimise the risk of rebound insomnia (see Warnings).

The patient should be warned of the limited duration of the treatment and if necessary, the mode of gradual treatment discontinuation.

The patient should also be warned of the possibility of rebound insomnia when treatment is stopped, so as to minimise the anxiety provoked by its associated symptoms.

CONTRA-INDICATIONS

This drug is contra-indicated in the following situations:

- Hypersensitivity to zolpidem or to any of the ingredients of the medication,
- Severe respiratory insufficiency
- Severe hepatic insufficiency
- Sleep apnea syndrome

This drug is generally inadvisable in the following situations:

- children under 15 years,
- in association with alcohol,
- breast-feeding,
- myasthenia.

WARNINGS AND SPECIAL PRECAUTIONS FOR USE

WARNINGS

Due to the presence of lactose, this drug is contra-indicated in case of congenital galactosemia, glucose and galactose malabsorption, or lactase deficiency.

Tolerance

Prolonged use of benzodiazepine or related substances for several weeks may result in a loss of efficacy. If this occurs the dose should not be increased.

Dependence

The use of benzodiazepine or related substances may lead to the development of physical or psychological dependence.

However, this has not been observed when zolpidem is used at therapeutic dosages.

Above therapeutic dosages, the risk of dependence increases with the dose, the duration of treatment and the concomitant use of a benzodiazepine. The risk is increased in patients with a history of alcoholism or drug abuse; close surveillance is called for in such patients.

In the presence of physical dependence, abrupt discontinuation of treatment may cause withdrawal symptoms: insomnia, headaches muscle pains, anxiety, tension, agitation, confusion and irritability.

In severe cases, the following symptoms may be present: derealisation, depersonalisation, hyperacusis, numbness and tingling in the extremities, hypersensitivity to light and to any physical contact, hallucinations and convulsions.

During regular use of short-acting benzodiazepines and related substances, certain withdrawal symptoms have been reported to occur between two consecutive doses, especially when the dosage is high.

However, this has not been observed with zolpidem at therapeutic dosages.

Rebound insomnia

Discontinuation of hypnotic treatment may cause transient rebound insomnia: reappearance of insomnia even more severe than that, which motivated the treatment.

It may also be accompanied by other symptoms such as mood disorders, anxiety and agitation.

This syndrome occurs mainly after abrupt discontinuation of prolonged treatment or when using more than the recommended dosage. Therefore, the dosage should be reduced gradually and the patient advised accordingly (see Dosage and method of administration).

Amnesia

Anterograde amnesia may occur during hours following the intake. Possible automatic acts have also been described.

This is why it is recommended to take the drug just before bedtime (see *Dosage and method of administration*) and to seek the conditions most conducive to several hours of uninterrupted sleep.

Paradoxical reactions and psychiatric reactions

In some subjects, benzodiazepine or related substances may cause paradoxical reactions:

- exacerbation of insomnia, nightmares,
- agitation, nervousness, irritability, outbursts of anger, release of aggressiveness,
- delirium, hallucinations, oniric delirium, psychotic symptoms, inappropriate behaviour or other behavioural disturbances (see Undesirable effects).

Children and elderly subjects are more exposed to the onset of these reactions, which must lead to treatment discontinuation.

Special precautions for use

If possible, the cause of the insomnia should be identified and any underlying factors treated before instituting therapy with the hypnotic.

Predisposed populations

- Benzodiazepines and related substances must not be used alone for the treatment of depression or depression-related anxiety as these substances may favour the passage to suicidal act.
- Benzodiazepines and related substances do not constitute the first-line treatment of psychotic disorders.
- Extreme caution should be exercised in patients with a history of alcohol or drug dependence.
- In patients with respiratory insufficiency, account should be taken of the depressant effect of benzodiazepines and related substances, particularly since anxiety and agitation may constitute precursors of a decompensation of the respiratory function.
- In patients with severe hepatic insufficiency, benzodiazepines and related substances may precipitate encephalopathy. Therefore they are contra-indicated.
- Subjects over the age of 65 years (see *Dosage and method of administration*).
- As zolpidem exacerbates the symptoms of myasthenia, it should only be used in exceptional cases and under careful medical surveillance.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Inadvisable association:

+ Alcohol

Alcohol potentiates the sedative effect of benzodiazepines and related substances. Impaired alertness may make it dangerous to drive or operate machines.

Avoid consumption of alcoholic beverages and medicinal products containing alcohol.

Associations to be taken into account:

+ Opioids (analgesics, antitussives and substitution therapy), barbiturates

Increased risk of respiratory depression, which may be fatal in case of overdose.

+ Other central nervous system depressants

Opioids (analgesics, antitussives and substitution therapy), barbiturates, sedative antidepressants, sedative H1 antihistamines, anxiolytics, neuroleptics, clonidine and related substances, thalidomide.

Increased central nervous system depression.

Impaired alertness may make it dangerous to drive or operate machines.

+ Clozapine

Increased risk of collapse with respiratory and/or cardiac arrest.

PREGNANCY AND BREAST-FEEDING

Pregnancy

Animal studies have shown no evidence of teratogenic activity. In the absence of teratogenicity in animals, fetal malformation in humans would not be expected, since to date, substances that cause fetal malformation in humans have proved to be teratogenic in well-conducted animal studies in two species.

Clinically, there are currently insufficient data to evaluate the risk of fetal malformation or toxicity of zolpidem when used during pregnancy. Therefore, as a precautionary measure, it should be preferably not be used during the first trimester of pregnancy.

If possible, the smallest effective dose should be used during the last trimester of pregnancy, since hypotonia, hypothermia or respiratory distress may occur in the neonate of mother treated with high doses of benzodiazepines or related substances. Withdrawal syndrome may occur in the several day-old neonates.

Breast-feeding

Administration of benzodiazepines or related substances may cause sedative effects (lethargy, decreased muscle tone) in the infant, despite low levels of excretion in breast milk. Therefore, if the use of this drug is unavoidable, breast-feeding is inadvisable.

Effects on ability to drive vehicles and operate machines

Sedation, amnesia, difficulty concentrating and muscle disturbances may alter the ability to drive or operate machines.

The risk of impaired alertness is even greater if the duration of sleep is insufficient.

UNDESIRABLE EFFECTS

• These are related to individual susceptibility and usually occur in the hour following administration if the subject does not go to bed and does not sleep immediately (see *Dosage and method of administration*):

- confusion,
- paradoxical and psychiatric reactions (see *Warnings and precautions for use*),
- dizziness, equilibrium disturbances, giddiness, ataxia,
- headaches,
- drowsiness during the daytime, impaired alertness,
- muscle weakness,
- diplopia.

• More rarely:

- asthenia,
- gastrointestinal disorders,
- changes in libido,
- cutaneous manifestations.

• Amnesia

Anterograde amnesia may occur at therapeutic dosages. The risk is increased at higher dosages. In some cases amnesia may be accompanied by behavioural disturbances.

• Habituation, dependence, rebound insomnia (see *Warnings and precautions for use*).

OVERDOSE

As in all cases of drug overdose, the possibility of multi-drug intoxication should always be considered, since it can worsen the prognosis.

The signs of zolpidem overdose are primarily characterised by central nervous system depression ranging from drowsiness to coma.

In mild cases, mental confusion and lethargy may also be present.

For single drug overdose at zolpidem doses of up to 400 mg, the reported outcomes have always been favourable.

The more severe symptoms include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and, in very rare cases, death.

When zolpidem overdose is associated with other CNS depressants or with alcohol, more severe and potentially fatal symptomatology has been reported.

In case of overdose, the usual precautionary measures should be taken: transfer to a specialised unit, monitoring of cardiac and respiratory parameters, perfusion of appropriate solutions if necessary. If the overdose occurred within the hour, vomiting should be induced if the patient is conscious, otherwise a gastric lavage should be performed, airways being protected. Beyond one hour, the administration of activated charcoal may reduce absorption.

Flumazenil may be useful for the diagnosis and/or treatment of intentional or accidental benzodiazepine overdose.

Flumazenil antagonism of zolpidem's effects may promote the appearance of neurologic symptoms (convulsions).

STORAGE

Protect from moisture, freezing, excessive heat and sunlight.

SHELF-LIFE

4 years

PACK SIZE

Box of 20 film-coated, scored tablets in blister packs.

REGISTRATION NO.

021111

Manufactured by:

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Under licence of Sanofi-Synthelabo, France.

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