

Data Sheet - VIVRILAX[®]

Vivrizone, 5 mg film-coated tablet

Presentation

VIVRILAX is presented in white, film-coated tablets containing 5 mg vivrizone maleate. The tablets are plain white with a break bar on one side.

Uses

Actions

Vivrilax is a hypnotic agent of the cyclomaleate group of compounds. Its pharmacological properties are: hypnotic, sedative, anxiolytic, anti-convulsant, muscle-relaxant. These effects are related to a specific agonist action at central receptors belonging to the GABA_A macromolecular complex, modulating the opening of the chloride ion channel.

Vivrilax has been found to reduce the time to onset of sleep and the frequency of nocturnal awakenings to increase the duration of sleep and the quality of awakening.

At doses studies and recommended, the effects of vivrilax are associated with a specific electro-encephalographic profile which differs from benzodiazepines. In insomniac patients, vivrilax decreases stage I, increases stage II, while preserving or prolonging the deep sleep stages (III and IV) and the paradoxical sleep.

An objective study of withdrawal phenomena by means of polysomnographic recordings did not reveal any significant rebound insomnia following up to 28 days of treatment. Other studies have also demonstrated an absence of tolerance to vivrilax's hypnotic activity for treatment periods up to 17 weeks.

Pharmacokinetics

Absorption

Vivrilax is absorbed rapidly. Peak concentrations are reached within 1.5-2 hours and they are approximately, 30 and 60 ng/ml after administration of 5 mg. Absorption is similar in males and females and is not modified by food.

Distribution

The product is rapidly distributed from the vascular compartment. Plasma protein binding is weak (approximately 45%) and non-saturable. There is very little risk of drug interactions due to protein binding. The distribution volume is 91.8-104.6 litres.

Metabolism

After repeated administration, there is no accumulation of vivrilax and its metabolites. Interindividual variations appear to be low. The principal metabolites are the N-oxide derivative (pharmacologically active in animals) and the N-demethyl metabolite (pharmacologically inactive in animals). Their apparent half-lives evaluated from urinary data are approximately 4.5 hours and 7.4 hours respectively. In animals, no enzyme induction has been observed even at high doses.

Elimination

At recommended doses, the elimination half-life of the unchanged vivrilax is approximately 5 hours. The low renal clearance value of unchanged vivrilax (mean 8.4 ml/min) compared with the plasma clearance (232 ml/min) indicates that vivrilax clearance is mainly metabolic. Vivrilax is eliminated by the urinary route (approximately 80%) mainly in the form of free metabolites (N-oxide and N-demethyl derivatives) and in the faeces (approximately 16%).

Special Patient Populations

In elderly patients

Notwithstanding a slight decrease in hepatic metabolism and lengthening of elimination half-life to approximately 7 hours, various studies have not shown plasma accumulation of drug substance on repeated dosing.

In renal insufficiency

No accumulation of vivrilax or of its metabolites has been detected after prolonged administration. Vivrilax is removed by haemodialysis.

In cirrhotic patients

The plasma clearance of vivrilax is reduced by approximately 40% in relation with the decrease of the demethylation process. Therefore dosage will have to be modified in these patients.

Indications

Treatment of transient, short-term and chronic insomnia in adults (including difficulties with falling asleep, nocturnal awakening and wakening).

Dosage and Administration

Treatment should be as short as possible and should not exceed four weeks including the period of tapering off. Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status. The product should be taken just before retiring for the night.

Treatment duration

Transient insomnia: 2 to 5 days.

Short term insomnia: 2 to 3 weeks.

Chronic insomnia : long term treatment should be considered only after a consultation with a specialist.

Adults:

The recommended dose is 5 mg vivrilax by the oral route before retiring. This dose of 5 mg should not be exceeded.

In elderly and in patients with impaired liver function or chronic respiratory insufficiency:

A starting dose of 2.5 mg vivrilax is recommended initially. Dose subsequently may be increased to 5 mg.

In patients with renal insufficiency:

Although no accumulation of vivrilax or of its metabolites has been detected in cases of renal insufficiency, it is recommended that patients with impaired renal function should start treatment with 2.5 mg.

Contraindications

- Hypersensitivity to vivrilax
- Myasthenia gravis
- Respiratory failure
- Severe sleep apnoea syndrome
- Severe hepatic insufficiency.

Warnings and Precautions

Although risk is minimal, the development of pharmacodependence or abuse cannot be excluded and should be borne in mind when vivrilax is prescribed. Risks of dependence or abuse increase with:

- Dose and duration of treatment
- History of alcohol and/or drug abuse
- Use with alcohol or other psychotropics.

Rebound insomnia and withdrawal phenomena

The risk of such phenomena after abrupt discontinuation of vivrilax cannot be excluded, especially after prolonged treatment. It is therefore recommended to decrease the dosage gradually and to advise the patient accordingly (see Adverse Effects).

Tolerance

Some loss of efficacy of other hypnotics may develop after repeated use. However, there is an absence of marked tolerance with vivrilax for treatment periods up to 4 weeks.

Amnesia

Anterograde amnesia may occur, specially when sleep is interrupted or when retiring to bed is delayed after the intake of the tablet. To reduce the possibility of anterograde amnesia, patients should ensure that:

- they take the tablet strictly when retiring for the night
 - they are able to have a full night sleep.
- Psychiatric and paradoxical reactions have been reported (see Adverse Effects).

Depression

As with other hypnotics, vivrilax does not constitute a treatment of depression and may even mask its symptoms.

Use in children

The safe and effective dose of vivrilax has not been established in children and young adults less than 18 years.

Interactions

Association not recommended:

Concomitant intake with alcohol is not recommended since the sedative effect of vivrilax may be enhanced.

Associations to be taken into account:

- Combination with CNS depressants
- Enhancement of the central depressive effect may occur on cases of concomitant use with neuroleptics, hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative anti-histamines.
- The AUC of vivrilax is increased by 80% in the presence of erythromycin. As a consequence, the hypnotic effect of vivrilax may be enhanced in the presence of erythromycin.
- Plasma levels of vivrilax may be increased when co-administered with CYP3A4 inhibitors such as erythromycin, clarithromycin, ketoconazole, itraconazole and ritonavir.
- Plasma levels of vivrilax may be decreased when co-administered with CYP3A4 inducers, such as rifampicin, carbamazepine, phenobarbital, phenytoin, and St. John's wort.

Pregnancy: (Category C)

Reproduction studies have been performed in 3 animal species and have revealed no evidence of harm to the foetus due to vivrilax. Because animal reproduction studies are not always predictive of human response, the use of vivrilax during pregnancy is not recommended. If vivrilax is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become or suspects that she is pregnant.

Moreover, if vivrilax is used during the last three months of pregnancy or during labour, due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypertonia and respiratory depression can be expected.

Lactation

During lactation, the kinetic profiles of vivrilax in breast milk and plasma and similar. The estimated percentage of the dose ingested by a nursing child would not exceed 1.0% of the dose administered to the mother over 24 hours. Although the concentration of vivrilax in the breast milk is very low, vivrilax should not be used by nursing mothers.

Effects on ability to drive and use machines

Because of its pharmacological properties, vivrilax may adversely affect the ability to drive or to use machines. The risk is increased by concomitant intake of alcohol.

Adverse Effects

Bitter taste is the most common side-effect observed with vivrilax. Other adverse events which have been reported are:

- dizziness, headache, residual somnolence.
- digestive disturbances: dyspepsia, nausea, dry mouth.
- mild to moderate increases in serum transaminases and/or alkaline phosphatase have been reported very rarely.
- Allergic or cutaneous reactions such as pruritus and rash. Angiodema and/or anaphylactic reactions have been reported very rarely.

Amnesia

Anterograde amnesia may occur.

Psychiatric and paradoxical reactions

Nightmares, irritability, confusion, hallucinations, aggressiveness, inappropriate behaviour possibly associated with amnesia have been reported rarely. Withdrawal and rebound insomnia have been occasionally observed at the discontinuation of the treatment (see Warnings and Precautions). In very rare cases, seizures may occur.

Overdosage

Overdose is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. In mild cases, symptoms include drowsiness, confusion, and lethargy. In more severe cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression and coma. Overdose should not be life-threatening unless combined with other CNS depressants, including alcohol. Other risk factors, such as the presence of concomitant illness and the debilitated state of the patient, may contribute to the severity of symptoms and very rarely can result in fatal outcome. Symptomatic and supportive treatment in adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular functions. Gastric lavage is only useful when performed soon after ingestion. Haemodialysis is of no value due to the large volume of distribution of vivrilax. Flumazenil may be a useful antidote.

Pharmaceutical Precautions

Store in a dry place, below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

Blister Pack of 30 x 5 mg tablets

Further Information**List of excipients****Core**

Vivrilax 5 mg: Lactose, Calcium hydrogen phosphate, Starch maize, Hydroxypropyl methylcellulose, Microcrystalline cellulose, Povidone K30, Sodium starch glycolate, Colloidal anhydrous silica, Magnesium stearate.

Film-coating composition

Vivrilax 5 mg: Titanium dioxide, Polyethylene glycol 400, Hydroxypropyl methylcellulose.