

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sedoxil, 1 mg, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mexazolam 1 mg.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SEDOXIL is indicated for the management of anxiety disorder associated or not to psychoneurotic conditions.

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Dosage should be individualised according to the age of patient and severity of symptoms.

Adults: average dose is 1 – 3 mg daily, preferably divided in three doses.

Elderly patients: do not exceed 1,5 mg daily.

Children: Not for paediatric use.

Treatment of anxiety should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall duration of treatment generally should not be more than 8-12 weeks including the tapering off process. In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without revaluation of the patient's status with special expertise.

In any case treatment should be started with the lowest recommended dose.

In case of a missing dose after more than 1 hour as scheduled do not take it. Do not double the dose.

The patient should be checked regularly observed at the start of the treatment in order to decrease if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

4.3 Contraindications

Hypersensitivity to mexazolam or to any of the excipients. Myasthenia gravis, hypersensitivity to benzodiazepines, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.

4.4 Special warnings and special precautions for use

Dependence

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment, and is also greater in patients with a history of drug abuse or alcoholism. Once physical dependence has developed, abrupt termination of the drug will be accompanied by withdrawal symptoms; these may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound of anxiety

A transient syndrome, whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced aggravated form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of rebound phenomena is greater after abrupt discontinuance of the drug, it is recommended that the dosage be decreased gradually.

Duration of treatment

It should be as short as possible, depending on the indication, but should not exceed 8-12 weeks in case of anxiety, including tapering off process. Extension beyond this period should not take place without reevaluation 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. The patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur.

When benzodiazepines with a long duration of action, as mexazolam, are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms might develop.

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients would ensure that they would be able to have an uninterrupted sleep of 7-8 hours (see Undesirable Effects).

Paradoxical and psychiatric reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusions, rage, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur when benzodiazepines are used. Should this occur, use of the drug should be discontinued. These reactions are more like to occur in children and the elderly. Paradoxical reactions were reported in schizophrenic patients.

Specific patient groups

Elderly patients should be given a reduced dose (see dosage). A lower dosage is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Benzodiazepines are not indicated for patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide might be precipitated in such patients).

Benzodiazepines should be used with extreme caution in patients with a history of drug abuse and alcoholism.

SEDUXIL should be used with caution in patients with cardiac, renal or hepatic disorders and in patients with encephalic organic disorders.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended - concomitant intake with alcohol.

The sedative effect may be enhanced when SEDUXIL is used in combination with alcohol; this affects the ability to drive or use machines.

Take into account the association with CNS depressants.

Enhancement of the central depressive effect may occur in cases of concomitant use of SEDOXIL with antipsychotic (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic products, anaesthetics, and antihistamine sedatives.

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

In pre-clinical trials with animals the following interactions were reported:

Drugs enhancing mexazolam effects: chlorpromazine, haloperidol, diazepam, cyproheptadine, aminopyrine, phenobarbital, ethanol, sulpiride, trichlormethiazide and alpha-methyldopa.

Drugs antagonising mexazolam effects: imipramine, amitriptyline and chlorpheniramine.

Drugs, which have not shown interaction with mexazolam: diphenylhydantoin, scopolamine butylbromide, gefarnate, propranolol and pindolol.

4.6 Pregnancy and lactation

Pregnancy and lactation: Although pre-clinical trials on animals did not suggest any harm of mexazolam during pregnancy, its safety in humans was not established during pregnancy.

Benzodiazepines may cause congenital abnormalities when administered in the first trimester of pregnancy. If for compelling reasons SEDOXIL is administered during the late phase of pregnancy or during labour at high doses, effects on the neonate such as hypothermia, hypotonia and moderate respiratory depression can be expected.

Infants born to mothers who took benzodiazepines chronically during pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Since mexazolam may be found in the breast milk, it should not be given to breast feeding mothers.

Every woman of childbearing potential should contact the physician if she intends to become or suspects that she is pregnant.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function resulting from the administration of SEDOXIL may adversely affect the ability to drive or use machines.

If insufficient sleep duration occurs the likelihood of impaired alertness may be increased.

4.8 Undesirable effects

The most frequent side effects of benzodiazepines are likely to be an extension of the pharmacological actions and include drowsiness during the day, numbed emotions, reduced alertness, confusion, fatigue, headache, light-headedness, muscle weakness, ataxia or double vision.

Rarely (<0,1%) the following adverse events were reported with mexazolam: altered tongue movements, hypotension, light-headedness, nausea, vomiting, anorexia, gastric discomfort, gastric pain, abdominal pain, diarrhoea, hypersensitivity reactions (e.g. skin reactions), decreased libido, increase of alkaline phosphatase, anaemia and leukopenia. Commonly (0.1- 5%) were reported drowsiness, vertigo, dizziness, headache, ataxia, dry mouth, weakness, increases of aspartate aminotransferase, alanine aminotransferase and gamma - glutamyl transpeptidase.

Side effects occur predominantly at the start of therapy and usually disappear upon continued administration.

Amnesia

Anterograde amnesia may occur using therapeutic doses of benzodiazepines, the risk increasing when higher doses are used. Amnesic effects may be associated with inappropriate behaviour (see precautions).

Depression

Pre-existing depression may recur when benzodiazepines are used.

Psychiatric and paradoxical reactions.

Reactions like restlessness, agitation, irritability, aggressiveness, delusions, rage, nightmares, psychoses, inappropriate behaviour and other related adverse behavioural effects are known to occur

and become particularly severe with benzodiazepines. They are more likely to occur in children and the elderly.

Dependence

Even at therapeutic doses, SEDOXIL may lead to the development of physical dependence – discontinuance of the therapy may result in withdrawal or rebound phenomena (see precautions). Psychic dependence may also occur. Abuse of benzodiazepines has been reported.

4.9 Overdose

As with other benzodiazepines, overdose should not present a threat to life, unless combined with other CNS depressants, including alcohol.

In the management of overdose it should be borne in mind that multiple agents might have been taken. Following overdose with SEDOXIL vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken (if an endotracheal tube is in place) if the patient is unconscious, to prevent aspiration of vomiting. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce SEDOXIL absorption. Special attention should be paid to respiratory and cardiac functions and the patient should be closely observed in an intensive care unit. Overdose of benzodiazepines is usually manifested by central nervous system depression, ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy, and in more serious cases, symptoms include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Flumazenil, a specific benzodiazepine receptor antagonist, may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification: N05 BA

SEDOXIL is a benzodiazepine. As a rule, benzodiazepines act as central nervous system depressants capable of producing all levels of depression, from mild sedation to hypnosis and coma, depending on the dose.

The exact sites and mode of action have not been fully elucidated, but it appears to be mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), by the stimulation of specific receptors. Both GABA and chloride may enhance the binding to those receptors.

Sedative effects - it was shown in mice, rats and monkeys that mexazolam causes a higher inhibition on conflict behaviour, violence, aggressiveness and excitation than diazepam. Studies in cats and rabbits suggest that those sedative effects may result from the drug action upon the limbic system, including amygdala and hypothalamus.

Anticonvulsant effects - it was shown in mice, rats and monkeys that mexazolam causes a higher inhibitory effect on bemegride- and pentetrazol-induced convulsions than diazepam.

Myorelaxant effects – mexazolam inhibited the decerebrate stiffness and depressed the activity of gamma-motor neurones in cats.

Effects on motor function – Studies in mice, rats and dogs on the influence of mexazolam upon motor function (for example, inhibition of the spontaneous motor function, myorelaxant effect, inhibition of righting reflex and ataxic effect) showed that the effect is limited.

5.2 Pharmacokinetic properties

Following oral administration of mexazolam, the unchanged drug is not detected in blood. Only some active metabolites CND (chlornordiazepam) and COX (chloroxazepam) are found. It is suggested that mexazolam may be hydroxylated in the liver and conjugated through metabolic pathways, one of benzodiazepine-type (active metabolites) and the other of benzophenone-type (inactive metabolites). The CND is the main plasmatic metabolite of mexazolam. With a single dose of mexazolam, CND maximum serum concentration is attained after 1-2 hours. The distribution apparent volume is 150 L.

The used pharmacokinetic model is of bicompartimental type. Following repeated administration, the half-lives of CND and COX is large (130-200 h).

CND and COX protein binding is > 90%.

Less than 10% of the mexazolam dose administered orally is eliminated as metabolites in urine, given that most of the drug is excreted through the bile. The COX represents > 50% of the total amount of excreted metabolites, and is essentially found as conjugate.

5.3 Preclinical safety data

Studies held in several animal species, including mice, rats, rabbits, dogs and monkeys indicated a broad safety profile and a very low toxicity. In fact, the LD₅₀ for oral use was 4.687 mg/kg in the rat, 8.100 mg/kg in the Wistar-Imamichi rat and 1400 mg/kg in the Fischer rat.

In subacute toxicity studies in rats (10, 30, 125, 250, 500 and 1500 mg/kg, orally, 5 weeks) mortality was observed only in the group receiving 1500 mg/kg. Hypertrophy of hepatocytes occurred with similar doses or higher than 250 mg/kg, but disappeared after drug discontinuation. Mexazolam administered orally along 26 weeks to rats that received daily doses of 2, 10, 50 or 125 mg/kg have shown that the weight of liver, kidneys and adrenal glands increased in females of the group receiving the highest dose. Moreover, the histological exam has not shown significant changes. Changes in copulation or fertility of male rats were not detected (2, 10 or 20 mg/kg during 9 weeks); either lethal or teratogenic effects in the foetuses of female rats were not detected (2, 10 or 20 mg/kg, from the 14th day before copulation up to the 7th day of gestation). The administration of mexazolam during the period of organogenesis (rat - 2, 10 or 20 mg/kg/day during 11 days; rabbit – 0.04, 0.2, 1 or 5 mg/kg/day during 13 days) hasn't caused death or teratogenic effects in rat embryos and foetuses. The administration of mexazolam during the perinatal period and lactation (rats- 2, 10 or 20 mg/kg/day during 4 weeks from the 17th day of gestation) hasn't caused changes during the labour, lactation or in the sucklings (external abnormalities, post-natal time differentiation and reproduction capacity). Mexazolam didn't exhibit mutagenic potential *in vitro*, in the test of reversion and Rec-assay. The antigenicity of mexazolam was investigated in guinea pigs and rabbits, and no evidence of antigenicity was shown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, Maize starch, Hydroxypropyl cellulose, Calcium stearate, Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister PVC/Alu: 5 years.

Blister Alu/Alu: 4 years.

6.4 Special precautions for storage

Store in the original container.

6.5 Nature and contents of container

Blisters of Alu/Alu or PVC/Alu. Packs of 10, 20, 30, 40 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling <and disposal>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

BIAL – Portela & C^a, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

8. MARKETING AUTHORISATION NUMBER(S)

MA004/00201

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18th October 2005

10. DATE OF REVISION OF THE TEXT

10/2023