Stedon

Diazepam

Anxiolytic - Tranquiliser

Safety & efficacy

adelco

- Enhancement of neurotransmission inhibition through the GABA
- Manages stress and insomnia
- Muscular relaxant and anticonvulsant effects
- Immediate and prolonged action
- Does not reduce activity in working patients

Stedon

Diazepam

SUMMARY OF PRODUCT CHARACTERISTICS
S T E D O N
(DIAZEPAM)

1. NAME OF THE PHARMACEUTICAL PRODUCT
STEDON
2. QUALITATIVE AND QUANTITATIVE COMPOSITION IN ACTIVE INGREDIENT
STEDON TAB 2 mg: Diazepam 2 mg / TAB
STEDON TAB 5 mg: Diazepam 5 mg / TAB
STEDON TAB 10 mg: Diazepam 10 mg / TAB
STEDON INJ. SOL.: Diazepam 10 mg / 2 ml AMP

3. PHARMACEUTICAL FORM
Tablets 2 mg: White, flat tablets, on one side scored and with the inscription ''ADELCO'' on the other.
Tablets 5 mg: Green, flat tablets, on one side scored and with the inscription ''ADELCO'' on the other.
Tablets10 mg: Pink, flat tablets, on one side scored and with the inscription ''ADELCO'' on the other.
Injection Solution 10 mg / 2 ml: Slightly yellowish solution in dark colored ampoules.

4. CLINICALPARTICULARS
Diazepam belongs to the group of benzodiazepines.

4.1 Therapeutic indications
As an anxiolytic, it is indicated for the short-term treatment of anxiety and insomnia. It is also used in cases of alcohol withdrawal syndrome as adjunctive therapy.
As an antiepileptic, it is indicated for the control of status epilepticus.
As a muscle relaxant, it is indicated for muscle hypertonia or spasticity such as muscle spasms of topical etiology, upper motor neuron lesions, athetosis, stiff-man syndrome, tetanus. It is also indicated in akathisia syndrome caused by neuroleptics treatment.
Benzodiazepines are also indicated for preanesthesia, induction of anesthesia, sedation of patients operated with local anesthesia, conscious sedation, diagnostic or therapeutic operations of short duration, cardioversion, management of spasms (eclampsia, tetanus).
Benzodiazepines are recommended only when the disorders are severe, causing disability or extreme distress to the patient.

4.2 Dosage and administration
Anxiety
The duration of treatment should be as short as possible.
The patient should be regularly re-examined and the necessity of continuation of the treatment should be evaluated, especially if the patient does not present any symptoms.
Generally, the total duration of treatment should not exceed 8-12 weeks, including tapering off process.
In special cases prolongation of treatment, beyond the maximum recommended duration, may be required. In this case, re-evaluation of the patient's condition by the physician is required.
Insomnia
The duration of treatment should be as short as possible.
Generally, the duration of treatment ranges from a few days to 2 weeks and maximum 4 weeks, including tapering off process.
In special cases prolongation of treatment, beyond the maximum recommended duration, may be required. In this case re-evaluation of the patient's condition by the physician is required.
In patients with impaired hepatic or renal function, reduction of the dose may be required.
As an anxiolytic
Adults: 2 mg 3 times daily, which may be increased to 15 - 30 mg daily in divided doses. After the first week of treatment, one dose at night is usually sufficient.
Elderly & Debilitated patients: half of the adults' dose.
As a hypnotic: 5 - 15 mg at night.
Intense anxiety or panic attacks, alcohol withdrawal syndrome: intravenously or intramuscularly 5 - 10 mg. The dose may be repeated after at least 3 - 4 hours. Intravenous administration should be performed very carefully and very slowly (not more than 5 mg / min).
It is doubtful whether intramuscular administration has an advantage over oral administration since absorption may not be normally achieved.
As a muscle relaxant
Adults: Orally: 2 - 10 mg, 3 - 4 times daily. The dose is increased and individualized depending on the patient's response and tolerance up to 60 mg daily.
Parenterally (intramuscularly or intravenously at a rate not greater than 5 mg / min): 10 mg which may be repeated after 4 hours.
Children: Orally: 0.1 – 0.8 mg/kg/24-hour in 3 - 4 doses. Parenterally: 0.1 - 0.2 mg/kg. In tetanus: 0.1 – 0.3 mg/kg intravenously every 1 - 3 hours.
As an antiepileptic (status epilepticus)
Intravenously: 0.15 - 0.25 mg/kg at a rate not faster than 0.5 ml (2.5 mg) per 30 seconds. The dose may be repeated after 30 - 60 minutes. Treatment may be continued by intravenous infusion of solution 0.008% (40 mg diazepam in 500 mg of dextrose 5% or sodium chloride 0.9%). The solution should be used within 6 hours. Maximum dose: 100 mg/ 24-hour (in children: 3 mg/kg). Part of the drug is absorbed on the plastic wall of the vial and the infusion device. This should be taken into consideration for the adjustment of dosage when infusion cannot be replaced by an intravenous injection. During intravenous injection, diazepam should not be mixed with other drugs.
Perioperatively
The dose is individualized depending on the age, the weight and the general condition of the patient. For preanesthesia: 0.1 - 0.2 mg/kg orally 1 - 1 ½ hour before surgery. For induction of anesthesia: 0.2 - 0.6 mg/kg intravenously.

4.3 Contraindications
- Myasthenia gravis
- Hypersensitivity to benzodiazepines
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Severe hepatic insufficiency

4.4 Special precautions and warnings during use
General
Due to Diazepam long action time, undesirable effects last for many hours after the last dose. For the same reason, cumulative effects may appear several days after initiation of the treatment, particularly in the elderly. Special caution is required when the drug is administered to patients with narrow angle glaucoma.
Benzodiazepines can cause dependence with withdrawal symptoms which appear after 1-2 days following treatment with short-acting benzodiazepine derivatives and after 2-5 days, or more, following treatment with long-acting benzodiazepine derivatives.
The intensity of these symptoms gradually increases after withdrawal and usually subsides after 1-3 weeks. The risk of dependence is higher and withdrawal symptoms are more intense with the more potent and short-acting derivatives at higher doses and for a longer period of administration. In order to avoid withdrawal syndrome, the daily dose should be gradually decreased at a rate of 1/4 – 1/8 of the daily dose every 1-2 weeks.
Intramuscular injection should be given slowly and deeply into the gluteal muscles. Intravenous injection should be given very slowly taking at least one minute for each 5mg (1ml) given. (1.0 ml solution per minute).The injection should be given directly into a large vein without being diluted with saline. Some experts recommend to flush the vein with normal saline 150-250ml or to resorb blood after the injection and to re-introduce it in the vein in order to flush it. This is considered as preventing the local thrombophlebitis due to diazepam precipitation.
Tolerance
After repeated administration for a few weeks, reduction of the hypnotic action of benzodiazepines may occur.
Dependence
The use of benzodiazepines can cause physical and psychic dependence.
The risk of dependence increases with dose and duration of treatment and is also higher in patients with a history of alcoholism or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may appear: derealization or depersonalization, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.
Rebound insomnia and anxiety: it is a transient syndrome in which the symptoms that led to the treatment with benzodiazepines recur in an intensified form, which may occur during treatment discontinuation. It may be accompanied by other reactions such as mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal or rebound phenomena is greater after abrupt discontinuation, treatment should be gradually discontinued.
Duration of treatment
The duration of treatment should be as short as possible (see 4.2 ''Dosage and administration'') depending on the indication, but should not exceed 4 weeks for insomnia and 8-12 weeks for anxiety cases, including tapering off process.
Treatment should not be continued beyond this period without re-evaluation of the patient's condition.
It is necessary to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be gradually decreased.
Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur while diazepam is being discontinued.
There are indications that in the case of short-acting benzodiazepines, withdrawal symptoms may appear during the intervals between doses, especially when the doses are high.
When long-acting benzodiazepines are administered, it is important to warn the patient that the transfer to short-acting benzodiazepines may cause withdrawal symptoms.
Amnesia
Diazepam may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours (see 4.8 ''Undesirable effects'').
Psychiatric and paradoxical reactions
When benzodiazepines are administered, the following reactions may appear:
restlessness, agitation, irritability, aggressiveness, illusions, mania, nightmares, hallucinations, psychotic disorders, inappropriate behavior and other behavioral disorders.
If any of these occur, the drug administration should be discontinued.
These reactions are more likely to occur in children and the elderly.
Special precautions for the excipients
STEDON INJ. SOL. contains Benzyl alcohol (30mg / 2ml). The maximum allowed exposure to this excipient is up to 90mg/kg/day. Specifically, the daily exposure to this substance is the accumulated daily dose of this excipient expressed or calculated as the sum of the administered or recommended daily dose of the medicinal product.
For exposure less than 90mg/kg/day it should not be given to premature infants or neonates. It may cause toxic and anaphylactic reactions to infants and children up to 3 years of age.
For exposure of 90mg/kg/day it should not be given to premature infants or neonates. Due to the risk of fatal toxic reactions caused by exposure to benzyl alcohol in quantities greater than 90mg/kg/day, the product should not be used in infants and children up to 3 years of age.
STEDON INJ. SOL. contains 11.5%vol ethanol (alcohol) i.e. 200mg/dose (2ml), equivalent to 2 ml of wine, 5ml of beer per dose. It is harmful for those suffering from alcoholism. This should be taken into consideration in pregnant or breast-feeding women, children and high risk groups such as patients with liver disease, or epilepsy.
STEDON INJ. SOL. contains propylene glycol. For parenteral administration and for exposure of 400mg/kg (adults) and 200mg/kg (children), it can cause symptoms similar to those of alcohol (Propylene glycol content: 900mg/2ml).
STEDON INJ. SOL. contains Benzoic acid E210 and Sodium Benzoate E211 and therefore, it can increase the risk of jaundice in newborn infants.
Tablets 10mg/tab contain Ponceau 4R E124 and therefore, allergic reactions may occur.
STEDON tablets contain Lactose Monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Special groups of patients
Children: Benzodiazepines should not be administered to children without careful assessment of the need for administration. The duration of treatment should be the shortest possible.
Elderly: The elderly receive a decreased dose (see 4.2 ''Dosage and administration'').
Also, lower dose is recommended in patients with chronic respiratory insufficiency due to the risk of respiratory depression.
Benzodiazepines should not be used in patients with severe hepatic insufficiency as they may precipitate encephalopathy.
Benzodiazepines should not be used for the primary treatment of a psychotic illness and should not be used alone in the treatment of depression or anxiety associated with depression due to the risk of precipitation of suicide in this patient group.
Benzodiazepines should be administered with great caution to patients with a history of alcoholism or drug abuse.

4.5 Interactions with other medicinal products and other forms of interaction
Not recommended: concurrent use with alcohol. The sedative effects are enhanced when the drug is used in combination with alcohol. This affects the ability to drive and use machines.
To be taken into consideration: co-administration with Central Nervous System depressants. Enhancement of the CNS depressant effect may be observed in case of co-administration with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressants, narcotics, analgesics, antiepileptics, anesthetics and tranquilizing antihistamines.
In the case of narcotic analgesics , enhancement of euphoria may occur resulting to an increase of psychic dependence. Drugs that inhibit specific hepatic enzymes (especially the cytochrome P450) may increase the effects of benzodiazepines

4.6 Pregnancy and lactation
Use during pregnancy
The drug should be avoided during pregnancy due to the risk and the undesirable effects on the neonate. If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.
If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labor at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.
Moreover, infants born to mothers who took benzodiazepines during the last trimester of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.
Use during lactation
Benzodiazepines are found in breast milk. They should not be administered to breast feeding mothers.

4.7 Effect on the ability to drive and use machines
Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased. (see 4.5 ''Interactions with other medicinal products and other forms of interactions'').

4.8 Undesirable effects
Somnolence, numbness, decreased alertness, confusion, fatigue, headache, vertigo, muscle weakness, ataxia or diplopia. These effects occur mainly at the beginning of the treatment and usually subside with repeated administration.
Sometimes other undesirable effects have been reported such as gastrointestinal disorders, disorders of libido or skin reactions.
In intravenous administration there is a risk of apnea or cardiac arrest or severe hypotension, especially in patients who are concurrently administered with barbiturates or paraldehyde. After an operation, benzodiazepines can cause prolonged intermittent amnesia, center and respiratory depression.
Amnesia
Anterograde amnesia may occur using therapeutic doses, the risk increases with higher doses. The symptoms of amnesia may be accompanied by inappropriate behavior (see 4.4 ''Special Precautions and Warnings during use'').
Depression
Preexisting depression is possible to appear during treatment with benzodiazepines.
Psychiatric and paradoxical reactions
When benzodiazepines are administered, the following reactions may appear:
restlessness, agitation, irritability, aggressiveness, illusions, mania, nightmares, hallucinations, psychosis, inappropriate behavior and other behavioral disorders.
These reactions are more likely to occur in children and the elderly.
Dependence
The use of benzodiazepines (even at therapeutic doses) can cause physical dependence.
Discontinuation of treatment may result into withdrawal or rebound phenomena behavior (see 4.4 ''Special Precautions and Warnings during use'').Psychic dependence may appear. Benzodiazepines abuse has been reported.

4.9 Overdosage
Overdosage is not life-threatening unless it is combined with other CNS depressants (including alcohol).
For the management of overdosage, the possibility of having taken multiple medication should be taken into consideration.
For the management of overdosage caused by orally administered STEDON, vomiting should be induced (within 1 hour), as long as the patient is conscious, or gastric lavage, after having protected the airways, if the patient is unconscious. If benefit from emptying the stomach is not expected, activated charcoal is given in order to reduce absorption.
Great caution is required regarding the respiratory and cardiovascular functions in an intensive care unit.
Diazepam overdose usually manifests with CNS depression of varying degree which ranges from somnolence to coma.
In mild cases symptoms include somnolence, mental confusion and lethargy. In more severe conditions ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death may occur.
Flumazenil may be used as an antidote.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC code: N05BA01
The pharmacological action of STEDON is exercised in the areas of hippocampus (limbic), thalamus, hypothalamus, neocortex and generally in the reticular formation. As a result of this pharmacological action, there is a reduction of anxiety in human and aggression in animals, calmness and facilitation to sleep. Additionally, STEDON has anticonvulsant action and improves muscle convulsion of limited or generalized form.
The therapeutic action of STEDON is achieved with the enhancement of neurotransmission inhibition which is achieved through the gamma-Aminobutyric acid (GABA). GABA is a major inhibitory neurotransmitter found in various areas of the central nervous system. Benzodiazepines facilitate the neurotransmission inhibition achieved by GABA. They do not modify the synthesis, release, binding or degradation of GABA.
Basically, GABA and benzodiazepines do not antagonize each other for their binding to GABA receptors, but benzodiazepines simplify and promote the GABA activity, before and after the synapses, through an allosteric mechanism, focusing on the GABA – receptors complex, also including the chloride anions modification of kinetics to the respective GABA channels (opening and closing). They do not however facilitate the GABA conductivity. The anatomical sites of action of benzodiazepines are not precisely determined.
It is, however, reported that their anxiolytic activity is limited at the hippocampus and the neocortex, the anticonvulsant to GABA receptors at the brain stem and the spinal cord and their sedative and anticonvulsant activity is limited at the hippocampus (limbic) neocortex and with a cerebral reticular formation.
STEDON does not appear to have any peripheral autonomous blocking activity, nor any extrapyramidal undesirable effects, despite the fact that, when administered in animals at higher doses it causes transient ataxia symptoms.
Long term administration of diazepam in experimental animals (rats) does not cause any side-effects on the endocrine glands. In dogs, transient cardiovascular suppression is observed.

5.2 Pharmacokinetic properties
a. General characteristics
Orally administered diazepam is rapidly absorbed within 1-3 hours. Absorption during intramuscular administration is similar. Diazepam binding to plasma proteins is high, at the level of 80%. Diazepam is metabolized to its main metabolite, Desmethyldiazepam, the half life of which is less than the one of the parent drug. The half life of diazepam ranges from 27-37 hours and the one of its basic metabolite from 50 to100 hours.
Following its administration, diazepam has a high distribution volume, which is higher in people with a high body fat value (women), given the diazepam lipophilic property. In men, however, who have a lower body fat value compared to their body weight, diazepam distribution volume is lower. Diazepam distribution volume explains the shorter duration of the drug 's activity, observed after the initial or after more than one therapeutic doses of the drug during the initiation of treatment. This phenomenon is milder when multiple drug doses are administered during a period of time of 1-2 weeks.
The half – life of diazepam increases with age, and this is due to the reduction of the enzyme conducting the liver N-methylation of the benzodiazepine in the liver. In general, the drug clearance in the body ranges between 0.38 ± 0.06 ml/minute /kg of body weight.
b. Patients characteristics
In certain patients, particularly at the beginning of treatment, the administration of multiple doses per 24 hours may be required until the desired therapeutic result is achieved. After the evaluation and determination of the required therapeutic dose, then, the total required dosage may be administered in one, single dose. Other patients, however, may require multiple daily doses. In people suffering from a difficulty to sleep, the single dose or part of the multiple drug doses administered per 24 hours, may be administered before bedtime.

5.3 Preclinical safety data
The oral lethal dose of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats. The intra-peritoneal administration of 400 mg/kg in a monkey caused the death of the animal on the 6th day following administration.
Acute toxicity
Rarely, respiratory depression, apnea and cardiac arrest have occurred, following IV administration of diazepam. These phenomena are observed in the elderly, in severely ill and debilitated patients or in people with impaired respiratory function or patients who are concurrently receiving other CNS depressants or alcohol. The IV administration of diazepam may cause local pain and thrombophlebitis.
The administration of diazepam during the last 15 hours of labor, especially in premature infants, may cause difficulty in breathing, apnea, hypothermia, lactation disorders and neuromuscular weakness in the neonate.
Chronic toxicity
When benzodiazepines, including diazepam, are administered without concurrent use of alcohol or other CNS depressants, they are well-tolerated with a wide range of safety, in cases of overdose.
Mutagenic action-oncogenesis
Not reported.
Reproductive toxicity
Diazepam crosses the placenta. Reproduction studies in rats with different oral doses of diazepam of 1, 10, 80 and 100 mg/kg are accompanied by reduction of the pregnancies and survival rates of neonates in test animals. In addition, at doses of 100 mg/kg, skeletal malformations of the ribs as well as congenital teratogenic abnormalities in rat fetuses and infants were observed.
Lower doses at the level of 80 mg/kg did not cause any skeletal or other teratogenic abnormalities in rat infants.
In humans, benzodiazepines administration during the first trimester of pregnancy may cause harelip or cleft palate. Nevertheless, this teratogenic complication of benzodiazepine, is not fully established.
Pregnancy
There are no full laboratory and clinical data regarding the safety evaluation of benzodiazepines during pregnancy. In general, since there is an increased risk of congenital malformations associated with the use of anxiolytic drugs, when administered intramuscularly or intravenously at doses over 30mg, during the last 15 hours of labor, the administration of diazepam and other benzodiazepines should be avoided during pregnancy, especially during the first trimester of pregnancy. Diazepam and its methylated metabolite cross the placenta during labor and cause respiratory disorders in the newborn, apnea, particularly in the premature newborns, hypothermia and lactation disorders. Withdrawal syndrome is observed in newborns whose mothers are physically addicted to benzodiazepines during the third trimester of pregnancy. Malformations e.g. harelip and cleft palate have been observed in cases of administration of the drug during the first trimester of pregnancy.
Lactation
Diazepam is excreted in breast milk, even in small quantities when the daily dosage does not exceed 10 mg. In case the administration of Diazepam during lactation is deemed absolutely necessary, close monitoring of the infant is required.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablets 2 mg: Lactose Monohydrate, Starch Maize, Acacia, Magnesium Stearate.
Tablets 5 mg: Lactose Monohydrate, Starch Maize, Acacia, Magnesium Stearate, Chlorophyll E140 CI 75810.
Tablets 10 mg: Lactose Monohydrate, Starch Maize, Acacia, Magnesium Stearate, Ponceau 4R E124 CI 16255
Injection Solution 10 mg / 2 ml: Propylene glycol, Sodium Benzoate, Benzoic acid, Ethanol 95%, Benzyl alcohol, Water for Injection

6.2 Incompatibilities
Alcohol, CNS depressants.

6.3 Shelf life
Tablets: 60 months
Solution for injection: 24 months

6.4 Special storage precautions
Keep at temperature below 25oC in a dry place, protected from light, out of reach and sight of children.

6.5 Nature and contents of the container
Tablets:
- BT x 30 (3 PVC/ALU blisters x 10 tabs)
- BT x 1000 (100 PVC/ALU blisters x 10 tabs)

Injection Solution:
- BT x 6 AMP x 2 ml
- BT x 10 AMP x 2 ml

(Not all packages may be marketed)

6.6 Instructions for use and handling
Not necessary.

6.7. Marketing Authorization Holder-Manufacturer
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7. MARKETING AUTHORIZATION NUMBER
STEDON 2 mg: 48125/08/16-01-2009
STEDON 5 mg: 48123/08/16-01-2009
STEDON 10 mg: 48121/08/16-01-2009
STEDON INJ. SOL., 10 mg / 2ml AMP: 48120/14-10-2008

8. DATE OF INITIAL AUTHORIZATION IN GREECE
1968

9. DATE OF LAST REVISION OF THE TEXT
01/2012

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