Doctor leaflet

1. NAME OF THE MEDICINAL PRODUCT

Bondormin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Bondormin tablet contains 0.25 mg brotizolam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
The tablet can be divided into 2 equal doses.

4. CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4.1 Therapeutic indications

Treatment of Insomnia.

4.2 Posology and method of administration

Posology
Unless otherwise prescribed, the usual dose is ½ - 1 tablet a day (equivalent to 0.125 - 0.25 mg brotizolam).

Treatment should be started with ½ a tablet a day (equivalent to 0.125 mg brotizolam). Depending on individual response, ½ a tablet a day (equivalent to 0.125 mg brotizolam) may be sufficient. The

maximum dose of 1 tablet a day (equivalent to 0.25 mg brotizolam) should not be exceeded because of the increased risk of adverse CNS effects.
In isolated cases (e.g. pre-operative sleep disturbances) the dose may be increased to 2 tablets.

Special populations:
A reduction in dosage to ½ a tablet a day should be considered in the following populations (see section 4.4):
- patients with impaired liver function (see section 4.3 and section 5.2)
- elderly and debilitated patients (see section 5.2)
- patients with chronic respiratory insufficiency with hypercapnia due to the risk of respiratory depression, especially at night (see section 4.3)
The tablets can be divided into equal halves for this purpose.

No dosage adjustment is normally necessary in patients with impaired renal function (see 5.2).

Paediatric population
Bondormin is contraindicated in children aged up to 18 years (see section 4.3).

Method of administration
Bondormin should be taken with a little liquid just before going to bed. To avoid affecting the onset and duration of action, Bondormin should not be taken on a full stomach.

Alternatively, the tablet may be allowed to dissolve under the tongue.

Sufficient time for sleep must be guaranteed to reduce the risk of affecting reactions (and hence the ability to drive) the following morning. Patients should therefore ensure that they will be able to sleep for 7 - 8 hours after taking a tablet.

Duration of treatment
Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to a maximum of two weeks. Treatment should be discontinued by gradual tapering, which should be tailored to the individual (see section 4.4). It should be borne in mind that discontinuation may initially cause rebound insomnia and that, in rare cases, restlessness, anxiety and tension may also occur.

In certain cases, extension beyond the maximum two-week treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

4.3 Contraindications

Bondormin is contra-indicated in:

- Patients with known hypersensitivity to brotizolam or other benzodiazepines or to any of the excipients listed in section 6.1
- Patients with myasthenia gravis.
- Patients with severe respiratory insufficiency.
- Patients with sleep apnoea syndrome.
- Patients with severe hepatic insufficiency.
- Patients with a history of dependence on alcohol, medicines or other drugs.
- Patients acutely intoxicated with alcohol, hypnotics, opiate-type analgesics or psychotropics (anti-psychotics, antidepressants, lithium).
- Pregnant women.
- Breast-feeding women.

- Children and adolescents up to 18 years of age, as safety and efficacy have not been investigated in this age group.
- Patients with any rare hereditary intolerance to any of the ingredients of the product (see 4.4).

4.4 Special warnings and precautions for use

Psychiatric conditions
Benzodiazepines should not be used alone for the treatment of psychotic illness.
Benzodiazepines alone are not suitable for the treatment of severe depression and should not be used alone for the treatment of anxiety associated with severe depression (suicide may be precipitated in such patients). Appropriate precautions must be taken when using benzodiazepines in severely depressed and suicidal patients.
Pre-existing depression may be unmasked.

Psychiatric and paradoxical reactions can occur during benzodiazepine treatment, particularly in the elderly. These reactions include restlessness, agitation, irritability, rages, nightmares, increased insomnia, hallucinations, psychoses, inappropriate behaviour, delirium and other adverse behavioural effects. Should this occur, use of the medicinal product should be discontinued.

Dependence
Chronic use of benzodiazepines may lead to the development of physical and psychic dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, insomnia, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealisation, depersonalisation, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Withdrawal symptoms may occur several days after discontinuation of treatment.

Use with alcohol
Concurrent use of brotizolam and alcohol can result in sedation, drowsiness and impaired concentration (see section 4.5).

Tolerance
Some loss of efficacy to the hypnotic effect may develop after repeated use for a few weeks.

Rebound anxiety and tension
Withdrawal of brotizolam treatment can lead to the development of a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form. The syndrome may be accompanied by mood changes, sleep disturbances and restlessness. Since the risk of withdrawal phenomena / rebound phenomena is greater after sudden dose reduction or abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Duration of treatment
The duration of treatment should be as short as possible (see 4.2). Extension beyond the recommended maximum treatment period 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. Moreover, 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 medicinal product is being discontinued.

Abrupt withdrawal of benzodiazepines can lead to the occurrence of paraesthesias, perceptual disturbances and depersonalisation, which may last for a week or more. Convulsions have been reported in a small number of cases.

Amnesia
In common with other benzodiazepines, brotizolam may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product.

Specific patient groups
Benzodiazepines have a muscle relaxant effect, which increases the risk of falls. Brotizolam should therefore be used with caution in the elderly.
Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.
Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

Bondormin contains lactose
Bondormin tablets contain 82.75 mg lactose monohydrate per tablet. Patients with the rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Bondormin.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol should be avoided during treatment with brotizolam as it modifies and increases the effects of brotizolam in an unpredictable manner (see 5.2).

Concurrent use of brotizolam and alcohol can result in sedation, drowsiness and impaired concentration (see 5.2, under "Alcohol").

Co-administration of brotizolam with other CNS depressants (antipsychotics (neuroleptics), antidepressants, hypnotics, anxiolytics/sedatives, narcotic analgesics, anaesthetics, anti-epileptics and sedative antihistamines) can lead to mutual enhancement of the CNS depressant effect and therefore requires very careful consideration.

Co-administration of brotizolam with narcotic analgesics can lead to enhancement of the euphoria and accelerate the development of dependence.

The nature and extent of interactions between brotizolam and other medicinal products (antidiabetics, antihypertensives, cardiac glycosides and hormones) varies unpredictably between individuals and caution is therefore required when giving Bondormin to patients taking these products.

Co-administration of brotizolam with muscle relaxants can increase the muscle relaxant effect.

Brotizolam is metabolised chiefly by the cytochrome P450 isoenzyme CYP 3A4 in the liver. Agents that compete with brotizolam for CYP 3A4 (competitive inhibition) and agents that inhibit CYP 3A4 can therefore increase the effect of brotizolam.
Known substrates for CYP 3A4 include astemizole, azole antifungals (such as itraconazole and ketoconazole), immunosuppressants (such as ciclosporin A, sirolimus and tacrolimus), calcium antagonists, macrolide antibiotics (such as clarithromycin and erythromycin), antimalarials (such as halofantrine and mefloquine), midazolam, pimozide, protease inhibitors (such as indinavir, nelfinavir and ritonavir), sildenafil, statins (such as atorvastatin, lovastatin and simvastatin), steroids (such as ethinyl-estradiol), tamoxifen and terfenadine.
Inhibitors of CYP 3A4, which can increase the toxicity of brotizolam, include azole antifungals, cimetidine, grapefruit juice, macrolide antibiotics and protease inhibitors.

Inducers of CYP 3A4, which increase enzyme activity and can reduce the effect of brotizolam, include carbamazepine, efavirenz, St. John's wort, nevirapine, phenobarbital, phenytoin, primidone, rifabutin and rifampicin.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no systematic data from the use of brotizolam in pregnant or breast-feeding women. Nonclinical studies have shown reproductive toxicity (see 5.3). Brotizolam should not be used during pregnancy or lactation.

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

If, for compelling medical reasons, brotizolam is administered during the late phase of pregnancy or during labour at high doses, effects on the neonate such as respiratory insufficiency, hypothermia, hypotonia and feeding difficulties ("floppy infant syndrome") can be expected.

If brotizolam is prescribed to a woman of child-bearing potential, she should be warned to contact her physician immediately if she intends to become or suspects that she is pregnant.

The risk of malformations following administration of therapeutic doses of benzodiazepines to women in the early phase of pregnancy appears to be low, although evidence from some epidemiological studies indicates an increased risk of cleft palate. There have been case reports of malformations and mental retardation in prenatally exposed children following benzodiazepine overdose or intoxication.

Lactation
Brotizolam and its metabolites are excreted in breast milk. There is therefore a risk of accumulation in the breast-feeding child. Accordingly, breast-feeding should be discontinued or interrupted on repeated administration of brotizolam to the mother.

Fertility
There are no clinical data on the effects of brotizolam on fertility. Nonclinical studies do not indicate harmful effects with respect to fertility (see 5.3).

4.7 Effects on ability to drive and use machines

Even when used in accordance with the prescribing instructions, this product may affect reactions and thus impair the ability to drive and operate machinery. Concurrent use of alcohol and/or medicinal products with CNS depressant activity will potentiate this impairment.

No studies on the effects of Bondormin on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects (see 4.8) such as sedation, amnesia and impaired psychomotor skills during treatment with Bondormin. Psychomotor impairment may increase the risk of falls and road traffic accidents.

Caution should therefore be recommended when driving a vehicle or operating machinery. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. If patients experience any of the above-mentioned undesirable effects, they should avoid potentially hazardous tasks such as driving a vehicle or operating machinery.

4.8 Undesirable effects

Most of the undesirable effects observed to date are related to the product's pharmacological activity. They occur predominantly at the start of therapy and usually decrease with continued administration.

The risk of dependence (in the form of e.g. a rebound effect, altered mood, anxiety and restlessness) increases with the duration of Bondormin treatment, which should not exceed two weeks.

The following definitions of frequencies are used:

Very common (≥ 1/10)
Common (≥ 1/100 up to < 1/10)
Uncommon (≥ 1/1.000 up to < 1/100)
Rare (≥ 1/10.000 up to < 1/1.000)
Very rare (< 1/10.000)
Not known (frequency cannot be estimated from the available data)

Psychiatric disorders	Uncommon	Nightmares, depression, altered mood, anxiety, drug dependence, emotional disorder, behavioural changes, agitation, changes in libido
	Rare	Confusion, restlessness
Nervous system disorders	Common	Light-headedness, headache
	Uncommon	Dizziness, sedation, ataxia, anterograde amnesia, dementia*, mental impairment*, impairment of psychomotor skills*
	Rare	Reduced alertness
Eye disorders	Uncommon	Diplopia
Gastrointestinal disorders	Common	Gastrointestinal disturbances
	Uncommon	Dry mouth
Hepatobiliary disorders	Uncommon	Liver disorders, jaundice
Skin and subcutaneous tissue disorders	Uncommon	Skin reactions
Musculoskeletal and connective tissue disorders	Uncommon	Muscle weakness
General disorders and administration site conditions	Uncommon	Withdrawal and rebound phenomena, paradoxical reactions, irritability, drowsiness
Investigations	Uncommon	Changes in liver function values
Injury, poisoning and procedural complications	Uncommon	Road traffic accidents*, falls*

*) Class effect of benzodiazepines

Brotizolam has a muscle relaxant effect and should therefore be used with caution in the elderly because of the risk of falls.

Abuse of benzodiazepine has been reported.

Withdrawal symptoms
Withdrawal and rebound phenomena may indicate development of dependence.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms such as headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.

In severe cases, derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures may occur (see 4.4).

Psychiatric and paradoxical reactions
Reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, vivid nightmares, hallucinations, psychoses and behavioural changes are known to occur when using benzodiazepines and benzodiazepine-like agents. They are more likely to occur in children and the elderly (see 4.4). Should this occur, use of the medicinal product should be discontinued.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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 with any medicinal product, it should be borne in mind that multiple agents may have been taken.

a) Symptoms
Overdose of benzodiazepines is usually manifested by various degrees of CNS depression. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

b) Management
Symptomatic measures are the mainstay of treatment.
Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.
Special attention should be paid to respiratory and cardiovascular functions, in an intensive care setting where appropriate.

If necessary, the specific benzodiazepine antagonist flumazenil may be used as an antidote. The Summary of Product Characteristics for flumazenil should be consulted prior to use.

Forced diuresis and haemodialysis are likely to be of limited value in pure brotizolam poisoning in view of the large volume of distribution of the substance and the fact that it is extensively bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives, benzodiazepines
ATC code: N05CD09

Brotizolam is a thienotriazolo diazepine derivative (hetrazepine) which binds specifically and with high affinity to benzodiazepine receptors in the CNS and which therefore exhibits the characteristic pharmacological properties of benzodiazepines.

It shortens sleep onset time, reduces nocturnal awakenings and increases total sleep time. At the recommended doses, changes in sleep architecture measured by electroencephalographic activity occurred: the mean duration and percentage of REM sleep were reduced during the first 6 hours of sleep.

In addition to its hypnotic effects, brotizolam demonstrated anxiolytic, sedative and muscle relaxant effects in animal studies.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, brotizolam is rapidly absorbed from the gastro-intestinal tract. After a single oral dose of 0.25 mg, a mean peak plasma concentration of 5.5 ± 0.7 ng/ml is achieved within 45 ± 12 min. Absorption is an apparent first-order process with a mean half-life of 14.9 ± 8.5 min. Absolute bioavailability following oral administration is about 70%

Distribution
Brotizolam is 89 - 95% bound to human plasma proteins and has an apparent distribution half-life of between 7 and 26 min.
The areas under the plasma concentration-time curve (AUC) range from 31.0 ± 5.7 ng·h/ml to 56.6 ± 21.3 ng·h/ml. Brotizolam is well distributed throughout the human body; the mean apparent volume of distribution is about 0.66 l/kg. In animals, brotizolam crosses the placental barrier and is excreted in the milk.

Biotransformation
Brotizolam is metabolised in the liver by CYP 3A4-mediated oxidative reactions; hydroxylation at various sites on the molecule (the methyl group and the diazepine ring) is the preferred metabolic pathway.
All the hydroxylated metabolites are virtually completely conjugated with glucuronic and/or sulphuric acid. These metabolites are less active than the parent compounds and it is assumed that they do not contribute to the clinical effect.

Elimination
Following oral administration of brotizolam, about two-thirds of a dose is excreted renally; the remainder is excreted via the faeces. Less than 1% of the dose is excreted in the urine as the parent compound. The major metabolites of brotizolam, α-hydroxybrotizolam and 6-hydroxybrotizolam, can be detected in the urine at concentrations of 27% and 7% respectively. Other highly polar metabolites whi-ch are presumed to have more than one hydroxyl group, as well as a substance which is less polar than brotizolam, can also be detected in the urine.

The mean elimination half-life of brotizolam from plasma is short and varies between 3 and 8 h in healthy subjects. Brotizolam has been classified as a short-acting benzodiazepine. The mean apparent oral clearance values for brotizolam following an oral dose of 0.25 mg range from 128.36 to 188.37 ml/min. The differences observed can be attributed to the methods of determination used (RIA and GLC). Repeated daily doses of 0.25 mg did not lead to accumulation or to any change in the pharmacokinetics of brotizolam compared to administration of a single dose.

Specific patient groups:

Elderly
Following oral administration of 0.25 mg, the mean time to peak plasma concentration was slightly higher in elderly patients (mean age 82 years) than in younger subjects (mean age 23 years) (1.7 h vs. 1.1 h). The mean peak concentration in elderly patients after an oral dose of 0.25 mg is about 5.6 ng/ ml, which is no different from the concentrations found in studies in young healthy subjects. The eli-mination half-life following oral administration is significantly longer in elderly patients than in you-ng volunteers (9.1 h vs. 5.0 h; $P < 0.02$). The absolute bioavailability of brotizolam in elderly patients is about 66%. Following continuous administration of a 0.25-mg dose of brotizolam over three weeks, neither accumulation nor faster elimination was observed. The pharmacokinetics of brotizolam are linear up to a dose of 1.5 mg.
Renal impairment
The pharmacokinetics of brotizolam are essentially the same for all patients with renal impairment irrespective of their creatinine clearance values (< 15 ml/min, 15 - 45 ml/min or 45 - 80 ml/min). The mean plasma elimination half-lives for patients with mild, moderate and severe renal insufficiency were 8.15 h, 6.90 h and 7.6 h respectively.

Hepatic impairment
In patients with hepatic cirrhosis, the peak absorption time and peak concentration of brotizolam are similar to those observed in healthy subjects, whilst the protein binding and clearance of unbound brotizolam are lower; the mean elimination half-life in patients with hepatic cirrhosis is 12.8 h (9.4 - 25 h).

Alcohol
Concurrent alcohol consumption significantly reduces the clearance of brotizolam (1.85 ml/min/kg vs. 2.19 ml/min/kg), increases peak plasma concentrations (5.3 ng/ml vs. 4.3 ng/ml) and prolongs the terminal elimination half-life (5.2 h vs. 4.4 h).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and single- and repeated-dose toxicity.

Effects in preclinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to human use.

In embryotoxicity studies carried out in rats at doses up to 30 mg/kg/day and in rabbits at doses up to 9 mg/kg/day, brotizolam did not have any embryotoxic or teratogenic effects. In rats, embryotoxic effects were seen at maternotoxic doses of 250 mg/kg/day and above. Fertility was not impaired at dos-es up to 10 mg/kg/day. In a study on peri- and postnatal development in rats, sedation and reduced weight gain were seen in the dams and increased mortality was observed in the pups at doses $\geq$ 2.5 mg/kg/day (equivalent to 80 times the MRHD calculated on a body surface area basis (mg/m^2)). Results of in-vitro and in-vivo tests did not reveal any evidence of a mutagenic potential for brotizolam. Brotizolam did not show any carcinogenic potential in mice at doses up to 200 mg/kg/day. In the rat study, the NOAEL was 10 mg/kg/day. At 200 mg/kg/day, hyperplastic and neoplastic changes we-re seen in the thyroid, thymus and uterus but these were considered species-specific and therefore not relevant to use of the substance in man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Starch Corn, Cellulose microcrystalline, Sodium starch glycolate, Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage

Store below 25°C.

6.4 Nature and contents of containers

Packs of 10 or 20 tablets in blisters.
Not all pack sizes may be marketed.

6.5 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with national requirements.

7. REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301

8. REGISTRATION NUMBER

120 37 26021 12

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in April 2017.