Drugfield Pharmaceuticals Limited

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Broletan® Tablets (Bromazepam 1.5mg)

1. NAME OF THE MEDICINALPRODUCT

Broletan® (Bromazepam 1.5mg) Tablets

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each tablets contains Bromazepam 1.5mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solid-Tablets

4. Clinical particulars

4.1 Therapeuticindications

Broletan®(Bromazepam) is effective in the management of acute tension and anxiety states; difficulty in interpersonal contact, insomnia, anxious depressive reactions; functional disturbances in the cardiovascular, respiratory, gastro-intestinal and genitourinary systems.In addition to being used to treat anxiety or panic states, bromazepam may be used as a premedicant prior to minor surgery.

Posology and method ofadministration Posology

Important Dosage and Administration Instructions

As the effect of food on bromazepam absorption is unknown, doses should preferably be given on an empty stomach.

The maximum recommended dose is 60 mg daily.

Average dose for ambulatory patients: 3 mg two or three times daily. It is often an advantage to make the evening dose larger than other doses, or when the total dose is low (e.g. 3 or 6 mg), to give the total dose in the evening.

Severe hospitalized cases: 6 – 12 mg two or three times daily.

These amounts are general recommendations, and dosage should be individually determined. Treatment of outpatients should begin with low doses, gradually increasing to the optimum level.

When treatment is ceased withdrawal should be gradual. The duration of treatment should be as short as possible.

The patient should be reassessed regularly and the need for continued treatment should be evaluated. The overall treatment should not be more than 2 – 4 weeks, followed by a tapering off process of up to 6 – 8 weeks.

Special Dosage Instructions

Bromazepam is not recommended in children as there is insufficient evidence of safety and efficacy in this group. Elderly patients and those with impaired hepatic function may require lower doses.

Method of administration

Oral Administration

4.2 Contraindications

Broletan® (Bromazepam 1.5mg) is contraindicated in patients with:
- known hypersensivity to benzodiazepines
- Severe respiratory insufficiency, including chronic obstructive airways disease with incipient respiratory failure
- Severe hepatic insufficiency as it may cause encephalopathy • Sleep apnea syndrome
- Myasthenia gravis.

4.3 Special warnings and precautions foruse

General

Patients should be checked regularly at the start of treatment in order to minimize the dosage and/or the frequency of administration, and to prevent overdose due to accumulation of bromazepam. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and concomitant use of BROLETAN and alcohol should be avoided. Such concomitant use has the potential to increase the clinical effects of BROLETAN possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression. Patients with known or presumed dependence on alcohol or drugs should not take benzodiazepines unless under medical supervision.

Duration of Treatment
In general, benzodiazepines should be prescribed for short periods only (e.g. 2 – 4 weeks).

Continuous long-term use of BROLETAN is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy, withdrawal symptoms can appear following the cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine). Following the prolonged use of BROLETAN at therapeutic doses, withdrawal from the medication should be gradual. An individualized withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from four weeks to four months have been suggested. As with

other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of BROLETAN.

Hypotension

Although hypotension has occurred rarely, BROLETAN should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Amnesia

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines. Anterograde amnesia may occur at therapeutic dosages with the risk increasing at higher dosages. Amnesiac effects may be associated with inappropriate behaviour.

Myasthenia Gravis

BROLETAN could increase the muscle weakness in myasthenia gravis and should not be used in patients with this condition (see CONTRAINDICATIONS).

Acute Narrow-angle Glaucoma

Caution should be used in the treatment of patients with acute narrow-angle glaucoma because of atropine-like side effects.

Impaired Renal/Liver Function and Blood Dyscrasias

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances, some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevation of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended.

Depression, Psychosis and Schizophrenia

BROLETAN is not recommended as primary therapy in patients with depression, anxiety and/or psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Preexisting depression may be unmasked during benzodiazepine use. Suicidal tendencies may be present or uncovered and protective measures may be required.

Paradoxical Reactions

Paradoxical reactions such as restlessness, agitation, irritability, rages, hallucinations, aggressiveness, delusion, nightmares, psychosis, inappropriate behavior and other adverse behavioral effects, acute rage, stimulation or excitement may occur; should such reactions occur, BROLETAN should be discontinued.

Impaired Respiratory Function

BROLETAN should be used with extreme caution in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension (see CONTRAINDICATIONS).

Epilepsy

When BROLETAN is administered to persons with convulsive disorders, an increase in the frequency and/or severity of grand mal seizures may occur, necessitating increased anticonvulsant medication. Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Hereditary Problems

As BROLETAN contains lactose, patients with rare hereditary problems such as galactose intolerance, Lapp lactase deficiency or glucose-galactosemalabsorption should not take this drug.

Abuse

Caution must be exercised in administering BROLETAN to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Dependence

The use of benzodiazepines may lead to dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the medicine. 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. Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour. Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines or changing to a benzodiazepine with a considerably shorter elimination half-life. These symptoms range from headaches, muscle pain, insomnia, tension, restlessness, confusion, irritability, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feeling of motion, metallic taste), hyperacusis, numbness and tingling of the extremities, epileptic seizures, depersonalization, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating (see ADVERSE EFFECTS). Such manifestations of withdrawal, especially the more serious ones, are more common in patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, BROLETAN should be terminated by tapering the dose to minimize occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication. Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pretreatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect reemergence of pre-existing symptoms combined with withdrawal symptoms. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 – 4 h) may experience relatively mild rebound symptoms in between their regular doses.
Withdrawal/rebound symptoms may follow high doses for relatively short periods. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation of treatment.

Effects on Ability to Drive or Operate Machinery

As with all patients taking CNS-depressant medications, patients receiving BROLETAN should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from BROLETAN therapy. Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or operate machinery. This is increased if the patient has taken alcohol concomitantly with BROLETAN. Abilities may be impaired on the day following use.

4.4 Interaction with other medicinal products and other forms ofinteraction

Clinically Significant Drug Interactions with Bromazepam

There may be an interaction between bromazepam and any of the following:

- alcohol
- antihistamines (e.g. cetirizine, doxylamine, diphenhydramine, hydroxyzine, loratadine)
- antipsychotics (e.g., chlorpromazine, clozapine, haloperidol, olanzapine, quetiapine, risperidone)
- aprepitant
- aripiprazole
- "azole" antifungals (e.g., itraconazole, ketoconazole, voriconazole)
- baclofen
- barbiturates (e.g., butalbital, phenobarbital)
- benzodiazepines (e.g., alprazolam, diazepam, lorazepam)
- buspirone
- calcium channel blockers (e.g., amlodipine, diltiazem, nifedipine, verapamil)
- carbamazepine
- chloral hydrate
- cimetidine
- deferasirox
- efavirenz
- ethinylestradiol (birth control pills)
- gabapentin
- medroxyprogesterone
- mexiletine
- mirtazapine
- muscle relaxants (e.g., cyclobenzaprine, methocarbamol, orphenadrine)
- narcotic pain relievers (e.g., codeine, fentanyl, morphine, oxycodone)
- olopatadine
- phenytoin
- primaquine
- proton pump inhibitors (e.g., lansoprazole, omeprazole)
- rifampin
- rifabutin
- quinolone antibiotics (e.g., ciprofloxacin, norfloxacin, ofloxacin)
- selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram, duloxetine, fluoxetine, paroxetine, sertraline)

- scopolamine
- St. Johns wort
- tapentadol
- theophylline
- topiramate
- tramadol

- gemfibrozil
- grapefruit juice
- isoniazid
- lamotrigine
- levetiracetam
- macrolide antibiotics (e.g., clarithromycin, erythromycin)
- tranylcypromine
- tricyclic antidepressasnts (e.g., amitriptyline, clomipramine, desipramine, trimipramine)
- vemurafenib
- zopiclone

If you are taking any of these medications, speak with your doctor or pharmacist. Depending on your specific circumstances, your doctor may want you to:

- stop taking one of the medications,
- change one of the medications to another,
- change how you are taking one or both of the medications, or
- Leave everything as is.

An interaction between two medications does not always mean that you must stop taking one of them. Speak to your doctor about how any drug interactions are being managed or should be managed.

Medications other than those listed above may interact with this medication. Tell your doctor or prescriber about all prescription, over-the-counter (non-prescription), and herbal medications you are taking. Also tell them about any supplements you take. Since caffeine, alcohol, the nicotine from cigarettes, or street drugs can affect the action of many medications, you should let your prescriber know if you use them.

Pregnancy

Risk Summary

Benzodiazepines cross the placenta and may cause hypotonia, reduced respiratory function and hypothermia in the new born infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of medicines. Infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period. If BROLETAN is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuing BROLETAN if she intends to become, or suspects that she is pregnant.

Lactation

Risk Summary

As benzodiazepines pass into breast milk, nursing mothers should not take BROLETAN. **Females**

and Males of Reproductive Potential

Infertility

There are no data available on male and female fertility changes in libido (changes in sexual desire or ability)

Paediatric Use

Benzodiazepines may impair mental alertness in children.

Bromazepam is not recommended for use in children due to insufficient evidence of safety and efficacy in this age group.

4.5 Effects on ability to drive and use machines

As with all patients taking CNS-depressant medications, patients receiving BROLETAN should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from BROLETAN therapy. Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or operate machinery. This is increased if the patient has taken alcohol concomitantly with BROLETAN. Abilities may be impaired on the day following use.

4.6 Undesirable effects

ADVERSE REACTIONS

Most adverse effects encountered with Broletan® have been referable to the central nervous system.

Post-marketing Adverse Reactions

Psychiatric Disorders: Confusional state, emotional disturbances, libido disorders, nervousness and depression have been reported. Paradoxical reactions such as restlessness, agitation, irritability, aggression, delusion, anger, nightmares, sleep disorders, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur with benzodiazepines or benzodiazepine-like agents. Should this occur, the use of Broletan® should be discontinued. Such reactions are more likely to occur in children and elderly patients than in other patients. Dependence: Chronic use (even at therapeutic doses) may lead to the development of physical and psychic drug dependence: discontinuation of therapy may result in withdrawal or rebound phenomena. Abuse of benzodiazepines has been reported.

Nervous System Disorders: Drowsiness and ataxia become less common with repeated administration. Headache, dizziness, decreased alertness, seizures, tremor, speech disorders and incontinence have been reported. Anterograde amnesia may occur using therapeutic dosages with the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Eye Disorders: Diplopia and blurred vision have been reported.

Gastrointestinal Disorders: Gastrointestinal disorders, dry mouth, nausea and vomiting have been reported.

Metabolic and Nutritional Disorders: Anorexia has been reported.

Skin and Subcutaneous Tissue Disorders: Skin reactions including pruritis and rash have been reported.

Musculoskeletal and Connective Tissue Disorders: Muscle weakness and muscle spasm have been reported.

Respiratory Disorders: Respiratory depression has been reported.

Cardiac Disorders: Cardiac failure including cardiac arrest, hypotension, tachycardia and palpitations have been reported.

Investigations: Instances of decreased haemoglobin and increased white cell counts have been reported.

4.7 Overdose

Bromazepam is commonly involved in drug overdoses. A severe bromazepam benzodiazepine overdose may result in an alpha pattern coma type. The toxicity of bromazepam in over dosage increases when combined with other CNS depressant drugs such as alcohol or sedative hypnotic drugs. Similarly to other benzodiazepines however, being a positive modulator of certain neuroreceptors and not an agonist, the product has reduced overdose potential compared to older products of the barbiturate class. Its consumption alone is very seldom fatal in healthy adults.

5. PHARMACOLOGICALPROPERTIES

Pharmacodynamics

Bromazepam is a benzodiazepine with anxiolytic action. In low doses, BROLETAN selectively reduces tension and anxiety. In high doses, sedative and muscle-relaxant properties appear. Its molecular structure is composed of a diazepine connected to a benzene ring and a pyridine ring, the benzene ring having a single nitrogen atom that replaces one of the carbon atoms in the ring structure. It is a 1, 4-benzodiazepine, which means that the nitrogens on the seven-sided diazepine ring are in the 1 and 4 positions.

Mechanism of Action

Bromazepam binds to the GABA receptor GABAA. This will facilitate GABA mediated chloride channel opening and produce hyperpolarization. This will produce an increase in the concentration of inhibitory neurotransmitter GABA and chloride ions and decreases firing rate of neurons. These alter normal excitatory functions of the body.

5.1 Pharmacokinetic properties

Absorption

Bromazepam, taken in the fasting state, is almost completely absorbed. Peak plasma levels of bromazepam are reached between 0.5 – 4 hours and may be maintained for up to 12 hours. The mean peak bromazepam level after a 12 mg oral dose is about 140 ng/mL. There is significant variation between subjects. The absolute (versus IV solution) bioavailability of the tablet is 60%. There is no information on the effect of food on absorption.

Distribution

On average, 70% of bromazepam is bound to plasma proteins, which is considerably less than for diazepam and is attributed to the increased polarity of the molecule due to the presence of the pyridyl radical. The volume of distribution is about 50 L.

Metabolism

Bromazepam undergoes extensive metabolism. The main metabolic pathway involves hydroxylation in position 3 with subsequent glucuronidation and cleavage of the heterocyclic ring with subsequent hydroxylation in the benzene ring and conjugation. Two metabolites predominate: 3-hydroxy-bromazepam and 2-(2-amino-5-bromo-3hydroxybenzoyl) pyridine.

Elimination

Less than 2% of a dose is excreted unchanged. The urinary recovery of intact bromazepam and the glucuronide conjugates of 3-hydroxy-bromazepam and 2-(2-amino-5-bromo-3hydroxybenzoyl) pyridine is 2%, 27% and 40% of the administered dose. Bromazepam has an elimination half-life of about 17 h (range 11 – 22 h). The clearance is about 40 mL/min.

Pharmacokinetics in Special Populations Elderly: The elimination half-life may be prolonged in elderly patients. The average reduction in clearance in elderly patients compared to young subjects is nearly 50%.

5.2 Preclinical safety data

Non-clinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6. PHARMACEUTICALPARTICULARS

6.1 List ofexcipients

1. Lactose Anhydrous
2. Corn Starch
3. Microcrystalline Cellulose
4. Polyvinyl Pyrrolidone K30
5. Magnesium stearate (Blending)

5.2 Incompatibilities

Not applicable

5.3 Shelf life

48 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Broletan® Tablet is presented in a 3 x 10 blisters with leaflet enclosed

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

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