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**Ihr Zeichen:**

### PHV issue: Bromazepam

Sehr geehrte Damen und Herren,

basierend auf der Evaluierung des PSURs im EU-HBD-worksharing Projekt (Verfahrensnummern: FR/H/PSUR/0066/001 / FR/H/PSUR/0066/002) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Bromazepam – hältigen Arzneispezialitäten aufzunehmen.



### 4.3 Contraindications

Bromazepam must not be administered to patients with known hypersensitivity to benzodiazepines, severe respiratory insufficiency, severe hepatic insufficiency (benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may cause encephalopathy), myasthenia gravis or sleep apnea syndrome.

### 4.4 Special warnings and precautions for use

#### *Amnesia*

Benzodiazepines 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 an uninterrupted sleep of several hours. Amnestic effects may be associated with inappropriate behaviour (see also 4.8 Undesirable Effects).

#### *Psychiatric and Paradoxical reactions*

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the medicinal product should be discontinued.

They are more likely to occur in children and the elderly.

#### *Duration of treatment*

The duration of treatment should be as short as possible (see 4.2 Posology) and should not exceed eight to twelve weeks, including tapering off process. Extension beyond these periods 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. 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.

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

#### *Concomitant use of alcohol / CNS depressants*

The concomitant use of bromazepam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of bromazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see 4.5 Interaction with other medicinal products and other forms of interactions).

The patient 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.

### *Tolerance*

Some loss of efficacy to the effects of benzodiazepines may develop after repeated use for a few weeks.

### *Specific patient groups*

Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.

Elderly should be given a reduced dose (see 4.2 Posology).

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Benzodiazepines are not indicated to treat 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 may be precipitated in such patients). Therefore, bromazepam should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (see section 4.5 Interaction with other medicinal products and other forms of interactions).

### *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; 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, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced 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 withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

If containing lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### *Pharmacodynamic Interaction*

Benzodiazepines produce an additive effect when co-administered with alcohol or other CNS depressants. Concomitant intake with alcohol is not recommended.

Bromazepam should be used with caution when combined with other CNS depressants. Enhancement of the central depressive effect may occur in case of concomitant use with antipsychotics (neuroleptics), anxiolytics/sedatives, some antidepressant agents, opioids, anticonvulsants, sedative H1-antihistamines.

Special care should be made with drugs depressing respiratory function such as opioids (analgesics, antitussives, substitutive treatments), notably in elderly people.

##### *Pharmacokinetic interaction*

Pharmacokinetic interactions can occur when bromazepam is administered along with drugs that inhibit the hepatic enzyme CYP3A4 by increasing the plasma levels of bromazepam.

The co-administration of bromazepam with strong CYP3A4 inhibitors (for example azole antifungals, protease inhibitors or some macrolides) should be made with caution and a substantial dose reduction considered. In the case of narcotic analgesics enhancement of euphoria may also occur, leading to an increase in psychic drug dependence.

#### **4.6 Pregnancy and lactation**

Although no specific clinical data are available for bromazepam, a large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found an increased risk of oral clefts. The data indicated that the risk of having an infant with an oral cleft after maternal benzodiazepine exposure is less than 2/1000 compared with an expected rate for such defects of approximately 1/1000 in the general population.

Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of foetal active movements and a variability of foetal cardiac rhythm.

When treatment has to be administered for medical reasons during the last part of pregnancy, even at low doses, floppy infant syndrome such as axial hypotonia, sucking troubles leading to a poor weight gain may be observed. These signs are reversible but they may last from 1 up to 3 weeks, according to the half life of the product. At high doses, respiratory depression or apnea

and hypothermia in newborn may appear. Moreover, neonatal withdrawal symptoms with hyperexcitability, agitation and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed.

Taking into account these data, the use of bromazepam during pregnancy may be considered, if therapeutic indications and posology are strictly respected.

If bromazepam treatment is necessary during the last part of pregnancy, high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in newborn.

Since bromazepam is transferred to breast milk, breast feeding is not recommended during treatment.

#### 4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also 4.5 Interactions). This effect is increased if the patient has taken alcohol.

#### 4.8 Undesirable effects

The following undesirable effects have been reported during treatment with bromazepam with the following frequencies:

Very common:  $\geq 1/10$ ;

Common  $\geq 1/100$  to  $< 1/10$ ;

Uncommon  $\geq 1/1,000$  to  $< 1/100$

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Undesirable effects
<i>Immune System Disorders</i>	
frequency not known	Hypersensitivity, anaphylactic shock, angioedema
<i>Psychiatric Disorders</i>	
frequency not known	Confusional state*, emotional disorder*, libido disorders, drug dependence**, drug abuse**, withdrawal syndrome**



	<p>Depression</p> <p>Paradoxical reactions such as restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, inappropriate behaviour**</p> <p>Anterograde amnesia**, memory impairment</p>
<i>Nervous System Disorders</i>	
frequency not known	Somnolence*, headache*, dizziness*, decreased alertness*, ataxia*
<i>Eye Disorders</i>	
frequency not known	Diplopia*
<i>Cardiac Disorders</i>	
frequency not known	Cardiac failure including cardiac arrest
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	
frequency not known	Respiratory depression
<i>Gastrointestinal Disorders</i>	
frequency not known	Nausea*, vomiting*, constipation
<i>Skin and Subcutaneous Tissue Disorders</i>	
frequency not known	Rash, pruritus, urticaria
<i>Musculoskeletal and Connective Tissue Disorders</i>	
frequency not known	Muscle weakness*
<i>Renal and Urinary disorders</i>	
frequency not known	Urinary retention
<i>General Disorders and Administration Site Conditions</i>	



frequency not known	Fatigue*
<i>Injury, Poisoning and Procedural Complications</i>	
frequency not known	Falls, fractures***

\* These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration

\*\* see section 4.4 Warnings and Precautions

\*\*\* The risk of falls and fractures is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

#### 4.9 Overdose

##### *Symptoms*

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of bromazepam is seldom life-threatening if the drug is taken alone, but may lead to slurred speech, areflexia, apnea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

##### *Treatment*

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

Further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil (Anexate®), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil (Anexate®), for further information on the correct use of this drug.

Oben angeführte Textabschnitte stellen eine Mindestanforderung dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.