SUMMARY OF PRODUCT CHARACTERISTICS FOR BENZODIAZEPINES AS ANXIOLYTICS OR HYPNOTICS

Guideline Title	**Summary of Product Characteristics for Benzodiazepines as Anxiolytics or Hypnotics**
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Additional Notes	**This guideline provides a framework for the preparation of a Summary of Product Characteristics (SPC) in accordance with Directive 65/65/EEC, for a medicinal product containing a benzodiazepine when used as an anxiolytic or a hypnotic.**

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SUMMARY OF PRODUCT CHARACTERISTICS FOR BENZODIAZEPINES AS ANXIOLYTICS OR HYPNOTICS

This guideline in general also applies to benzodiazepine-like agents (i.e. compounds which interact with the GABA-benzodiazepine reœptor complex). In that case throughout the text, benzodiazepines should be read as benzodiazepines and benzodiazepine-like compounds.

1. NAME OF THE MEDICINAL PRODUCT

To be completed by the company

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

To be completed by the company

3. PHARMACEUTICAL FORM

To be completed by the company

4 CLINICAL PARTICULARS

4.1 Therapeutic Indication

The following indications are acceptable if sufficient evidence is provided.

Anxiety

Insomnia

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

4.2 Posology

Anxiety

Treatment 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 a tapering off process.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without reevaluation of the patient's status with special expertise.

Insomnia

Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including tapering off process of four weeks.
In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without reevaluation of the patient's status.

For all products: treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

The dose for adults has to be completed by the company.

In addition to the normal dose for adults, a dose recommendation for the elderly and for patients with impaired liver and/or renal function must be given.

In case of rapid distribution it should be added, that the product should be taken just before going to bed.

In addition, for long acting benzodiazepines, it must be stated that the patient should be checked regularly 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. Contra indications

Myasthenia gravis Hypersensitivity to benzodiazepines Severe respiratory insufficiency Sleep apnoea syndrome Severe hepatic insufficiency.

4.4. Special Warnings and special precautions for use

Tolerance

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

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, 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.

Duration of treatment

The duration of treatment should be as short as possible (see Posology) depending on the indication, but should not exceed 4 weeks for insomnia and eight to twelve weeks in case of anxiety, 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.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

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.

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 7-8 hours (see also 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.

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 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).

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

4.5. Interactions

– Not recommended: Concomitant intake with alcohol

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

– Take into account: Combination with CNS depressants

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

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

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

4.6. Use during pregnancy and lactation

Statements under this heading will have to be evaluated for each compound. However, for all medicinal products the following should be mentioned.

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 labour 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 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.

Since benzodiazepines are found in the breast milk, benzodiazepines should not be given to breast feeding mothers.

4.7. Effects on ability to drive or to 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 Interactions).

4.8. Undesirable effects

Drowsiness (when the product is used as a hypnotic it should be stated explicitly: drowsiness during the day), numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. Other adverse reactions like gastrointestinal disturbances, changes in libido or skin reactions have been reported occasionally.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour. (see Warnings and precautions).

Depression

Pre-existing depression may be unmasked during benzodiazepine use.

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 or benzodiazepine-like agents. They may be quite severe with this product. They are more likely to occur in children and the elderly.

Dependence

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see Warnings and precautions). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

4.9. Symptoms and treatment of overdosage

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.

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 intensive care.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. 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.

Flumazenil may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A short description of the anxiolytic, sedative and hypnotic characteristics as well as the possible muscle relaxant and anticonvulsant characteristics should be given.

5.2 Pharmacokinetic properties

The following pharmacokinetic data should be listed:

– rate and extent of absorption

– time to reach maximum plasma level

– elimination half-life (both for the compound itself and its (active) metabolite, if any)

– volume of distribution

– protein binding.

If these data are available for elderly patients, they should be added.

For benzodiazepines or their metabolites with a long elimination half-life, the time required to reads steady state plasma levels should be added.