Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nitrazepam Tablets B.P. 5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrazepam B.P. 5 mg

3 PHARMACEUTICAL FORM

Round, flat-faced, white tablets, marked with a scoreline on one face and NITRAZEPAM 5” on the reverse.

4 CLINICAL PARTICULARS

Insomnia

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

4.1 Therapeutic Indications

Insomnia

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

4.2 Posology and method of administration

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.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

Adults: The usual dosage is 5 to 10 mg before retiring.

Elderly: The dose should be reduced to 2.5mg.

The product should be taken just before going to bed. 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 Contraindications

- Myasthenia gravis

- Hypersensitivity to benzodiazepines
- Severe respiratory insufficiently
- Sleep apnoea syndrome
- Severe hepatic insufficiency.

4.4 Special warnings and 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: derealization, depersonalization, 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 drug 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). Benzodiazpines should be used with extreme caution in patients with a history of alcohol or drug abuse.

4.5 Interaction with other medicinal products and other forms of interaction

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 analgestics, anti-epileptic drugs, 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 metabolized only by conjugation.

4.6 Pregnancy and lactation

Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbances in offspring exposed in utero.

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 later phase of pregnancy, or during labour, 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 mother.

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 sufficient 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 side effects 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 benzodiazepine or benzodiazepine-like agents. 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 Preactions).* Psychic dependence may occur. Abuse of benzodiazepines has been reported.

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 have been taken.

Following overdose with any medicinal product, 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

Nitrazepam is a typical benzodiazepine. It binds to benzodiazepine receptors in the brain thereby potentiating the inhibitory actions of gamma aminobutyric acid (GABA) in the spinal cord, brain stem, cerebellum, limbic system and cerebral cortex.

The potentiation of GABA inhibition diminishes the activity in ascending activating systems, particularly noradrenergic and serotonergic pathways from brain stem and mid-brain to the cerebral cortex. Sedation and muscle relaxant actions are typical of benzodiazepines and nitrazepam has also powerful anticonvulsant effects.

5.2 Pharmacokinetic properties

Nitrazepam is readily absorbed from the gastrointestinal tract with a rapid entry to the brain. The redistribution phase is fairly short, the decline in plasma concentrations being biphasic. The time to peak concentration is 0.5 - 4 hours. Traces are found in breast milk and nitrazepam crosses the placenta quite readily reaching fetal concentrations similar to those in the maternal plasma, in late pregnancy. The drug is extensively metabolised in the liver, with <4% of the dose excreted unchanged. Metabolites are excreted in the urine and about 20% of an oral dose is found in the faeces.

5.3 Preclinical safety data

Not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nitrazepam, Maize starch, Lactose, Snowflake 12701, Primojel (sodium starch glycollate), Talc (E553(b)) and Magnesium stearate (E572).

6.2 Incompatibilities

None stated.

6.3 Shelf Life

The shelf-life expiry date for this product shall not exceed three years from the date of its manufacture.

Do not use after the 'Use Before' date given on the pack.

6.4 Special precautions for storage

Store at a temperature not exceeding 25^0C.

6.5 Nature and contents of container

Polyethylene bottles with screw-cap.
1,000 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None.

7 MARKETING AUTHORISATION HOLDER

Worldwide Pharmaceutical Research Limited
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Ireland.

8 MARKETING AUTHORISATION NUMBER

PA 0565/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 18 April 1996