NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Frisium® 10mg Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of clobazam.

Excipient with known effect(s): Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

White, round, scored tablets marked B/GL with Hoechst logo on reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adjunctive therapy in partial or generalised epilepsy and monotherapy in certain forms of epilepsy such as Lennox-Gastaut and catamenial epilepsy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Small doses should be used initially, 5-15mg/day, gradually increasing to a maximum daily dose of 60mg/day, as directed by the doctor. The possible interference with alertness and reaction time must be taken into account. After improvement of the symptoms, the dose may be reduced. The fundamental principle is to keep the dose as low as possible. Constant doses, eg. 20mg/day and intermittent therapy, discontinuing clobazam and subsequently prescribing it again, have proved effective. If the daily dose is divided, the higher proportion should be taken at night.

Daily doses up to 30mg may be taken as a single dose at night.

Adults:

20 - 30 mg daily in divided doses or as a single dose at night. Maximum dose 60 mg.

Children and Elderly Patients:

Half the adult dose.

Children over 3 years and elderly patients receive half the daily dose recommended for adults. Clobazam should not normally be given to children between the age of 6 months and 3 years, unless it is strictly indicated.

In patients with impaired liver and kidney function, the dosage should be reduced. Increased responsiveness and higher susceptibility to adverse effects may be present in patients with renal or hepatic impairment, children and elderly patients and require low initial doses and gradual dose increments under careful observation (see Section 4.4 Special warnings and precautions for use). Benzodiazepines must not be given to children without careful assessment of the need for their use (see Section 4.3 Contraindications).

When clobazam is to be discontinued after prolonged administration, the dose should be tapered off over a period of time, including patients who have had poor response to therapy. There is an increased susceptibility to seizures as well as other withdrawal symptoms, when withdrawn suddenly.

Treatment with clobazam should not be continued for more than 4 weeks without medical supervision. At this time the patient should be re-assessed and regularly thereafter in order to evaluate the need for continued treatment.

4.3 CONTRAINDICATION

- Hypersensitivity to clobazam or other benzodiazepines or excipients.
- History of drug or alcohol dependence.
- Myasthenia gravis.
- Severe respiratory insufficiency or chronic obstructive airway disease with incipient respiratory failure.
- Sleep apnoea syndrome.
- Severe impairment of liver function.
- Pregnancy (see Section 4.6 Fertility, pregnancy and lactation - Pregnancy – Category C)
- Lactation (see Section 4.6 Fertility, pregnancy and lactation - Pregnancy – Category C)

Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months and 3 years, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Alcohol and CNS Depressant Drugs

Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of clobazam.

Clobazam may potentiate the effects of CNS depressant drugs, particularly sedation; therefore the administration of clobazam should be cautious in cases of acute intoxication with alcohol, hypnotics, analgesics, neuroleptics, antidepressants or lithium (see Section 4.5 Interactions with other medicines and other forms of interactions).

Opioids and Benzodiazepines

Concomitant use of opioids and benzodiazepines, including clobazam, may result in profound sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to the use of opioids alone. If a decision is made to prescribe clobazam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when clobazam is used with opioids (see Section 4.5 Interactions with other medicines and other forms of interactions).

Dependence and Tolerance

In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of Frisium is not recommended. The use of benzodiazepines may lead to physical and psychological dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. The risk of dependence increases with the dose and duration of treatment, however this can still occur when used within the therapeutic range. The risk of dependence is increased 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 anti-epileptic effect, may occur in patients receiving recommended dose under medical supervision. Tolerance to sedation may occur with benzodiazepines. In patients with a history of drug or alcohol dependence, there may be an increased risk of development of dependence with clobazam.

Withdrawal

After as little as one week of therapy, withdrawal symptoms can appear following the cessation of recommended doses. Following the use of Frisium at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for

each patient in whom dependence is known or suspected. The minimum time is probably four weeks, although programmes as long as four months have been suggested. As with all benzodiazepines, when treatment is suddenly withdrawn, a temporary increase of sleep disturbance can occur after use. A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (eg clobazam) to one with a short duration of action.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms range from headaches, sleep disturbances, increased dreaming, tension, restlessness, confusion, excitability, symptomatic psychoses (eg withdrawal delirium), numbness and tingling sensations in extremities, muscle pain, sweating, nausea and vomiting, hyperacusis, epileptic seizures, insomnia, anxiety, dysphonia, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations, (e.g. feelings of motion, metallic taste), depersonalisation, 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. 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 Frisium should be terminated by tapering the dose to minimise 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, mood changes, anxiety or sleep disturbances and restlessness mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

Abuse

Caution must be exercised in administering clobazam 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.

Use in elderly or debilitated patients

Dosage should be limited to the smallest effective amount to reduce the possibility of a fall due to sedation, giddiness, drowsiness, muscle weakness, confusion or ataxia.

Hypotension

Although hypotension occurs uncommonly, clobazam should be administered with care to patients in whom a drop in blood pressure may lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Epilepsy

When benzodiazepines are administered to persons with convulsive disorders, there is a possibility that the frequency and/or severity of seizures may increase and require an adjustment of anticonvulsant medication (development of tolerance). There is some evidence that concurrent administration of clobazam with phenobarbitone, phenytoin or carbamazepine may marginally increase the blood levels of the anticonvulsants and also increase the rate of metabolism of Frisium. Increases in valproic acid levels with clobazam treatment, have also been observed in a study involving six patients. Therefore the blood levels of the anticonvulsants should be determined in such cases. Abrupt withdrawal of benzodiazepine should be avoided, as this may temporarily increase seizure frequency and severity.

Amnesia

Amnesia, usually anterograde but extending sometimes to the period preceding drug administration, has been frequently reported after parenteral administration and less frequently after oral doses of benzodiazepines.

Paradoxical reactions

Paradoxical reactions such as rage, stimulation or excitement may occur rarely with clobazam and are an indication to discontinue the drug.

Thyroid adenomas

A dose related increase in thyroid adenomas was observed in a 2 year study in rats.

Muscle Weakness

Clobazam can cause muscle weakness. Therefore in patients with pre-existing muscle weakness or spinal or cerebellar ataxia, special observation is required and a dose reduction may be necessary. Clobazam is contraindicated in patients with myasthenia gravis .

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

Impaired Renal/Liver Function

In patients with impairment of renal and hepatic function, responsiveness to clobazam and susceptibility to adverse effects are increased, and a dose reduction may be necessary. In rare

instances some patients taking benzodiazepines have had elevations of liver enzymes. In long-term treatment renal and hepatic function must be checked regularly.

Blood Dyscrasias

In rare instances some patients taking benzodiazepines have developed blood dyscrasias. As with other benzodiazepines, periodic blood counts are recommended.

Depression, Psychosis and Schizophrenia

Clobazam is not recommended as primary therapy in patients with depression and 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. Suicidal tendencies may be present or uncovered and protective measures may be required.

Impaired Respiratory Function

Caution in the use of clobazam is recommended in patients with respiratory depression and in patients with chronic or acute respiratory insufficiency. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension. Respiratory function must be monitored and a dose reduction may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency (see Section 4.3 Contraindications).

Serious Skin Reactions

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with clobazam in both children and adults during the post-marketing experience. A majority of the reported cases involved the concomitant use of other drugs, including antiepileptic drugs, that are associated with serious skin reactions.

SJS/TEN could be associated with a fatal outcome. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment. Clobazam should be immediately discontinued when SJS/TEN is suspected. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

CYP2C19 Poor Metabolisers

In patients who are CYP2C19 poor metabolisers, levels of the active metabolite N-desmethyl-clobazam are expected to be increased as compared to extensive metabolisers. Dosage adjustment of clobazam may be necessary (e.g. low starting dose with careful dose titration).

Concomitant use of CYP2C19 inhibitors

The concomitant use of clobazam with CYP2C19 inhibitors, including cannabidiol containing medicinal products, dietary supplements and recreational products may result in increased exposure to N-desmethylclobazam (NCLB). Such increases might lead to increased adverse effects, such as somnolence and sedation. When used with medicinal products that are CYP2C19 inhibitors dosage adjustment of clobazam may be necessary. Dietary supplements and recreational products containing cannabidiol must not be taken in combination with clobazam as they contain unknown quantities of cannabidiol and are of variable quality (see Section 4.5 Interactions with other medicines and other forms of interactions and Section 5.2 Pharmacokinetic properties).

Suicidality

A meta-analysis of 199 randomised placebo controlled trials of Antiepileptic drugs (AEDs) (in monotherapy or adjunctive therapy) for various indications has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The results of this analysis were largely based on AED monotherapy in non-epilepsy indications. Clobazam was not part of the meta-analysis.

Based on this class effect, Frisium, as an AED, may increase the risk of suicidal thoughts or behaviour in patients with any indication.

Patients should be monitored for worsening of depression, suicidal thoughts or behaviour, and any unusual changes in mood or behaviour. This applies in particular to patients with a history of depression or suicidal ideation. Pre-existing depression may be unmasked during benzodiazepine use. In patients with anxiety associated with depression, Frisium must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepines (such as Frisium) alone can precipitate suicidal behaviour in such patients.

Several other epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with other benzodiazepines and hypnotics. There are very limited data available for clobazam in these studies.

Cases of suicidal behaviour have been reported with clobazam in post-marketing surveillance. However, in those cases, a causal relationship has not been established due to confounding factors or insufficient information.

Use in the Elderly

As the elderly have increased sensitivity to adverse reactions, dosage should be limited to the smallest effective amount to reduce the possibility of a fall due to drowsiness, dizziness, muscle weakness, sedation, giddiness, confusion or ataxia (see Section 4.2 Dose and method of administration and Section 4.8 undesirable effects).

Effects on laboratory tests

See Section 4.8 Undesirable effects.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

CYP 450 inhibitors

Frisium undergoes oxidative metabolism, and consequently may interact with disulfiram or cimetidine resulting in increased plasma levels of benzodiazepines. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with drugs that inhibit the cytochrome P-450 enzyme (mono-oxygenase) system (eg. either disulfiram, erythromycin or cimetidine); some patients may require a reduction in benzodiazepine dosage.

Central nervous system depressant drugs

The benzodiazepines, including clobazam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression e.g. barbiturates, alcohol, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, hypnotics, narcotic analgesics, anxiolytics, anticonvulsants and anaesthetics (see Section 4.4 Special warnings and precautions for use). Special caution is also necessary when clobazam is administered in cases of intoxication with such substances or lithium.

The anticholinergic effects of other drugs including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

CYP interactions

In vitro studies identified CYP 3A4 and 2C19 as the main isozymes involved in the oxidative metabolism of clobazam, and 2C19 further metabolises the active metabolite N-desmethylclobazam (N-CLB), highlighting potential interactions with known inducers or inhibitors of these isozymes.

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethyl-clobazam (N-CLB), the active metabolite of clobazam and dosage adjustment of clobazam may be necessary when co-administered with strong CYP2C19 inhibitors (e.g., cannabidiol containing medicinal products, fluconazole, fluvoxamine, ticlopidine) or moderate CYP2C19 inhibitors (e.g. omeprazole) (see Section 5.2 Pharmacokinetic properties).

Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of drugs metabolised by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol) may be necessary.

Anticonvulsants

Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together. ECG monitoring should be performed and serum level monitoring of the anticonvulsant be performed more frequently.

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, has been reported with benzodiazepine administration.

In patients receiving concomitant treatment with valproic acid, there may be a slight to moderate rise in plasma valproic acid concentration. Phenytoin plasma levels may rise if patients receive concomitant treatment with clobazam. Where possible, it is recommended that blood levels of concomitantly administered valproic acid or phenytoin be monitored.

Carbamazepine and phenytoin may cause an increase in the metabolic conversion of clobazam to the active metabolite N-desmethyl-clobazam.

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethyl-clobazam. Monitoring of blood levels is recommended.

Muscle Relaxants

The effects of muscle relaxants and nitrous oxide may be enhanced.

Narcotic Analgesics

If clobazam is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence.

Opioids

The concomitant use of benzodiazepines, including clobazam, and opioids increases the risk of profound sedation, respiratory depression, coma and death because of additive CNS depressant effects. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see Section 4.4 Special warnings and precautions for use), and follow patients closely for respiratory depression and sedation.

Alcohol

Patients should be advised of possible interaction, especially with alcohol, as bioavailability of clobazam can be increased by 50% and therefore lead to increased clobazam effects.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There has been no study done on effect of clobazam on human fertility.

Adequate fertility studies in animals are lacking. The available data shows no effects of oral clobazam on fertility in rats and mice.

Pregnancy - Category C

Benzodiazepines cross the placenta and may cause hypotonia, reduced respiratory function, respiratory depression (including respiratory distress and apnoea), hypothermia, hypotonia and feeding difficulties (signs and symptoms of so-called “floppy infant syndrome”) in the newborn 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 drugs. Appropriate monitoring of the newborn in the postnatal period is recommended.

Cases of reduced foetal movement and foetal heart rate variability have been described after administration of benzodiazepines during pregnancy.

Animal studies have demonstrated reproductive toxicity.

Clobazam must not be used in the first trimester of pregnancy and in women of childbearing potential not using contraception and is not recommended in the other stages of pregnancy. Frisium should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Women of childbearing potential should be informed of the risks and benefits of the use of clobazam during pregnancy.

If a woman plans a pregnancy or becomes pregnant, carefully evaluate the risks and benefits and whether treatment with Frisium should be discontinued. If Frisium treatment is to be continued, use Frisium at the lowest effective dose.

Breast-feeding

Clobazam may appear in the breast milk of nursing mothers and may cause drowsiness and feeding difficulties in the infant. For this reason, Frisium must not be used in breast-feeding women. Neonates are generally more susceptible to the toxic effects of benzodiazepines.

In limited studies, no effects on offspring development were reported following oral administration of clobazam to rats from late gestation to weaning.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Clobazam has been shown to have a less detrimental effect on psychomotor performance than 1,4 - benzodiazepines (diazepam, lorazepam) in experimental studies in volunteers at doses of 10 to 30mg/day.

However, as with all patients taking CNS-depressant medications, patients receiving Frisium should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from Frisium therapy. Abilities may be impaired on the day following use.

4.8 UNDESIRABLE EFFECTS

The most common adverse effect reported in the Frisium clinical trials was sedation/tiredness/drowsiness occurring in 32% as compared to 43% given diazepam and 22% on placebo. The following side effects occurred in more than 1% of patients in the reported double blind studies.

CARDIOVASCULAR

Hypotension (1.2%).

DERMATOLOGICAL

Rash (1.4%).

GASTRO-INTESTINAL

Dry mouth (3.2%), constipation (2.1%), diarrhoea (1.4%), nausea (1.3%).

NERVOUS SYSTEM

Sedation/tiredness/drowsiness (32%), dizziness/ataxia (8.2%), headache (3.6%), insomnia (1.8%), confusion (1.6%), slurred speech (1.6%), tremor (1.3%).

PSYCHIATRIC

Depression (3.5%), irritability (1.5%).

Clinical adverse experiences occurring since the drug was marketed or occurring in less than 1% of patients in the controlled studies are listed below.

GASTROINTESTINAL

Vomiting, decreased appetite.

GENERAL

Weight gain, sweating, hypothermia, hang-over, anorexia, slowed or indistinct speech (disorders of articulation), fatigue and fall.

Dependence and tolerance may develop especially with prolonged use.

GENITOURINARY

Decreased libido or loss of libido.

MUSCULOSKELETAL

Muscle aches and weakness, stiffness or spasm, unsteady movement, slowing of reaction time, fine tremor of fingers, unsteadiness of gait and other motor functions.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Urticaria, pruritus, rash, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis including some cases with fatal outcomes.

Photosensitivity reactions have been reported.

NERVOUS SYSTEM

Amnesia, euphoria, agitation, numbed emotions, memory impairment, anterograde amnesia, pre-existing depression may be unmasked during benzodiazepine use. Amnesia effects may be associated with inappropriate/abnormal behaviour.

Disturbance in attention and speech disorder have commonly been reported.

Impairment/altered state of consciousness, sometimes combined with respiratory disorders, may occur in rare cases, and sometimes persist for a considerable length of time. Cognitive disorders and abnormal behaviour have also been reported.

EYE DISORDERS

Visual disorders (Blurred vision, diplopia, nystagmus).

LABORATORY TESTS

Abnormal liver function tests and haematology.

RESPIRATORY

Respiratory depression, particularly in patients with pre-existing compromised respiratory function (eg bronchial asthma) or brain damage, respiratory insufficiency and respiratory failure may occur or deteriorate.

PARADOXICAL REACTIONS

Especially in the elderly and in children, paradoxical reactions may occur, such as restlessness, poor quality of sleep, difficulty in falling asleep or sleeping through, irritability, acute agitational states, anxiety, aggressiveness, delusion, anger, fits of rage, nightmares, hallucinations, psychotic reactions, suicidal tendencies, frequent muscle spasms, initial insomnia and insomnia. In the event of such reactions, treatment with Frisium must be discontinued.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Overdosage 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, coma and very rarely death. The risk of a fatal outcome is increased in cases of combined poisoning with other central nervous system depressants, including alcohol.

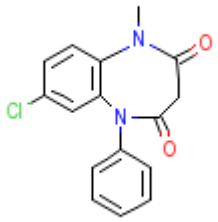
Treatment: In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken. Activated charcoal should be given to reduce absorption if the patient is conscious. Hypotension and respiratory depression should be managed according to general principles. Secondary elimination by forced diuresis, haemoperfusion or haemodialysis, are ineffective in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be useful in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

Contact the Poisons Information Centre on 0800 POISON or 0800 764 766 for advice on management of overdosage.

5 PHARMACOLOGICAL PROPERTIES

Clobazam is the first anxiolytic drug which belongs to the class of 1,5 rather than 1,4-benzodiazepines. Clobazam differs from the 1,4-benzodiazepines in that the nitrogen atoms in the 7-membered heterocyclic ring are located at positions 1 and 5 and an oxo substituent is located at position 4. This chemical difference confers both chemical and pharmacological properties upon clobazam which distinguish it from diazepam and other compounds of the 1,4-benzodiazepine series.

Chemical Structure



Molecular Formula: $C_{16}H_{13}ClN_2O_2$

Molecular Weight: 300.74

Chemical Name: 7-Chloro-1-methyl-5-phenyl-1,5-dihydro-3H-1,5-benzodiazepine-2,4-dione

CAS Number

22316-47-8

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anxiolytics of the benzodiazepine derivatives, ATC code: N05BA09.

Mechanism of action

Electrophysiological investigations have shown that the most important sites of action of the benzodiazepines are the limbic system, the thalamus and the spinal cord. At the synaptic level it has been proposed that various neurological systems including those utilising noradrenaline (norepinephrine), dopamine, serotonin, acetylcholine, glycine and gamma-aminobutyric acid (GABA) as neurotransmitters may be involved in the mediation of the pharmacological effects.

Evidence suggests that the observed decreased turnover rate of these various neurotransmitters can be explained in a unified way by a primary action of benzodiazepines on the GABA system through a facilitation of GABA-ergic neurotransmission. GABA is the major inhibitory neurotransmitter in the mammalian brain. In most brain regions GABA is the transmitter of postsynaptic inhibitions, but at certain brain stem synapses GABA mediates presynaptic inhibition. Benzodiazepines may enhance both of these actions of GABA.

Recent studies have demonstrated the presence of specific binding sites for benzodiazepines which are independent of GABA sites which occur exclusively in the central nervous system.

The concentration of the binding sites is highest in the cerebral and cerebellar cortex followed by areas of the limbic system, the basal ganglia and the brain stem. It remains to be demonstrated

whether benzodiazepine receptors are associated with GABA synapses or whether they show a wider pattern of distribution.

Like the 1,4-benzodiazepines, Frisium has been found to be an effective anti-anxiety agent and produces approximately equivalent anxiolytic activity compared to diazepam when used on a 2:1 dosage basis (Frisium: diazepam). Frisium produces almost no muscular relaxation at normal dosage levels.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Peak serum concentrations of clobazam occurred between one and four hours after oral administration, irrespective of the dose given. After a single 10 mg dose the peak serum concentration was found to be approximately 200 nanogram/mL. There are large differences between individuals in the levels reached. Approximately 85% of clobazam is bound to plasma proteins in the concentration range 50-10,000 nanogram/mL.

After oral administration of ^{14}C-labelled clobazam to man, approximately 90% of the radioactivity was recovered in the urine.

The presence of food delays but does not affect the extent of absorption.

Metabolism

Clobazam is demethylated by CYP 3A4, and to a lesser extent by 2C19 and 2B6 to form the active metabolite N-desmethyl-clobazam (N-CLB), which itself is further metabolised by CYP 2C19 into 4'-hydroxy-N-desmethyl-clobazam.

The main urinary metabolites are N-desmethyl-clobazam and 4'-hydroxy-clobazam. In man, the plasma elimination phase of unchanged clobazam varies with age and sex. In one study, after a single dose of 20 mg, the following half-lives were observed: young men 17 hours; young women 31 hours; elderly men 48 hours; elderly women 49 hours.

A steady level of clobazam in the plasma is reached within 1 week of initiating treatment or changing the dose. The plasma beta elimination phase of the major plasma metabolite, N-desmethyl-clobazam is considerably longer and is about 2 to 3 days for young men and women and 3 to 5 days for elderly men and women. It may increase with repeated doses. In a repeated dose study following administration of 10 mg clobazam twice daily for 28 days, the level of unchanged clobazam reached a steady state of 333 nanogram/mL within one week whereas the major serum metabolite took 28 days to reach a near steady state level about 8 times higher than that of unchanged clobazam and this was from 8.3 to 27.5 times higher than the metabolite level

after a single dose. The levels fell slowly after the last dose from 2,811 nanogram/mL to 2,031 nanogram/mL on the 7th day.

Age and sex influence the metabolism of clobazam in that the total clearance of clobazam is significantly lower in the elderly male and elimination half life is extended in both the elderly male and female which leads to the accumulation of the parent compound and its active metabolite. Lower dosage should be given to these patients.

Excretion

Over a two week period approximately 79% of a 20 mg oral dose of clobazam is excreted in the urine and 12% in the faeces as parent drug and/or metabolites.

Age and sex influence the metabolism of clobazam in that the total clearance of clobazam is significantly lower in the elderly male and elimination half life is extended in both the elderly male and female which leads to the accumulation of the parent compound and its active metabolite. Lower dosage should be given to these patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Clobazam was not genotoxic in a battery of *in vitro* (bacterial reverse mutation, mammalian forward mutation, chromosomal aberrations, unscheduled DNA synthesis) and *in vivo* (micronucleus test) assays.

Carcinogenicity

The carcinogenic potential of clobazam has not been adequately assessed. In a limited study in rats oral administration of clobazam at doses of 4, 20 and 100 mg/kg/day for two years found an increased incidence of thyroid follicular cell adenoma in males at the high dose (30 fold the 30 mg adult clinical dose based on body surface area), thought to be due to enhanced hepatic thyroxine clearance. A limited study on mice treated with clobazam for 80 weeks did not show evidence of increased tumour incidence.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Colloidal silicon dioxide
Lactose monohydrate
Magnesium stearate
Maize starch
Purified talc

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^{o}C.

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied in packs of 50 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Controlled Drug C5.

8 SPONSOR

sanofi-aventis new zealand limited
Level 8,
56 Cawley Street
Ellerslie
Auckland
New Zealand
Freecall: 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION OF THE TEXT

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SUMMARY OF CHANGES

Section changed	Summary of new information
All	datasheet has been aligned with approved AU PI dated 16/01/2020