

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Tapclob, 5mg/5ml Oral Suspension
Tapclob, 10mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tapclob 5mg/5ml Oral Suspension

Each 5ml of suspension contains 5mg of clobazam.

Each 5ml of suspension contains 1250mg of Sorbitol, 10.3mg of Sodium Methyl Hydroxybenzoate and 1.12mg of Sodium Propyl Hydroxybenzoate.

Tapclob 10mg/5ml Oral Suspension

Each 5ml of suspension contains 10mg of clobazam.

Each 5ml of suspension contains 1250mg of Sorbitol, 10.3mg of Sodium Methyl Hydroxybenzoate and 1.12 mg of Sodium Propyl Hydroxybenzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension

An off white viscous suspension with an odour of raspberry.

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, e.g. 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.

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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). Benzodiazepines must not be given to children without careful assessment of the need for their use (see Section 4.3).

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.

Method of administration

For oral use only

Once titrated to an effective dose of clobazam, patients should remain on their treatment and care should be exercised when changing between different formulations.

Interchangeability

The oral suspension is not interchangeable with other dose forms.

4.3 Contraindications

Hypersensitivity to clobazam or other benzodiazepines or any of the excipients of Tapclob Oral Suspension.

Myasthenia gravis.

Severe respiratory insufficiency or chronic obstructive airway disease with incipient respiratory failure.

History of drug or alcohol dependence.

Sleep apnoea syndrome.

Severe impairment of liver function.

Pregnancy (see Section 4.6)

Lactation (see Section 4.6)

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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

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 clobazam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from clobazam therapy. Abilities may be impaired on the day following use.

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. It is recommended that patients abstain from drinking alcohol during treatment with clobazam (increased risk of sedation and other adverse effects) (see Section 4.5).

Following the use of clobazam 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 rebound phenomenon or withdrawal syndrome may occur. The rebound phenomenon is characterised by a recurrence in enhanced form of the symptoms which originally led to clobazam treatment. This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness (see Section 4.4, Dependence). A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (e.g. clobazam) to one with a short duration of action.

In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of clobazam is not recommended. There is evidence that tolerance develops to the sedative effect 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).

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. A dose reduction is recommended.

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 clobazam.

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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 medicine 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 medicine.

Thyroid adenomas

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

Acute intoxication with CNS depressant drugs

Clobazam may potentiate the effects of CNS depressant medicines; therefore, the administration of clobazam should be cautious in cases of acute intoxication with alcohol, hypnotics, analgesics, neuroleptics, antidepressants and lithium (See Section 4.5).

In patients with pre-existing muscle weakness or spinal or cerebellar ataxia, special observation is required and a dose reduction may be necessary.

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

Opioids and Benzodiazepines

Concomitant use of benzodiazepines, including clobazam, and opioids may result in profound sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids 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 medicine-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).

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 (due to increased responsiveness to clobazam and susceptibility to adverse effects). In rare instances, some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver and kidney function tests 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

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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).

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 (see section 4.3).

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 medicines, including antiepileptic medicines, 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 medicine should not be resumed and alternative therapy should be considered.

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.

Dependence

The use of benzodiazepines may lead to physical and psychological dependence as defined by the presence of a withdrawal syndrome on discontinuation of the medicine. The risk of dependence increases with the dose and duration of treatment. However, the risk is present even with daily intake of clobazam over periods of only a few weeks, and applies not only to possible abuse with particularly high doses but also to the therapeutic dose 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 therapeutic effect seldom occurs in patients receiving recommended dose 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. These symptoms range from headaches, sleep disturbances, increased dreaming, tension, restlessness, confusion, excitability, symptomatic psychoses (e.g. 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,

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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, clobazam 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.

Use in the Elderly

In the elderly, due to the increase sensitivity to adverse reactions such as drowsiness, dizziness, muscle weakness, there is an increased risk of fall that may result in serious injury. Dose reduction is recommended and dosage should be limited to the smallest effective amount (see Section 4.2 and Section 4.8).

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).

Excipients in the formulation

Tapclob Oral Suspension contains sorbitol. Patients with a rare hereditary problem of fructose intolerance should not take this medicine.

The medicine also contains sodium methyl and propyl hydroxybenzoates which may cause allergic reactions. The signs may include a rash, swallowing or breathing problems and swelling of the lips, face, throat or tongue.

4.5 Interaction with other medicines and other forms of interaction

Clobazam 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 (e.g. either disulfiram, erythromycin or cimetidine); some patients may require a reduction in benzodiazepine dosage.

CYP 2C19 Inhibitors

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethyl-clobazam (N-CLB), the active metabolite of clobazam. Dosage adjustment of clobazam may be necessary when co-administered with strong (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors.

CYP 2D6 Substrates

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

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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, 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 caution is also necessary when clobazam is administered in cases of intoxication with such substances or lithium.

Anticholinergics

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

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.

In patients receiving concomitant treatment with valproic acid, there may be a slight to moderate rise in plasma valproic acid concentration. Similarly, 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.

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

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethyl-clobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels is recommended, prior to initiation of stiripentol, and then once new steady-state concentration has been reached, i.e. after 2 weeks approximately.

Alcohol

Patients should be advised of possible interaction as concomitant consumption of alcohol can increase the bioavailability of clobazam by 50% and therefore lead to increased clobazam effects.

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 and opioids increases the risk of profound sedation, respiratory depression, coma and death because of additive CNS depressant effects and actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA_A sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

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Muscle Relaxants

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

Effect on Laboratory Tests

Data not available.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

Benzodiazepines cross the placenta and may cause hypotonia, reduced respiratory function, respiratory depression (including respiratory distress and apnoea), which may be associated with other disorders such as sedation signs, hypothermia, hypotonia and feeding difficulties in the newborn (signs and symptoms of so-called “floppy infant syndrome”). Moreover, infants born to mothers who have taken benzodiazepines over longer periods during the later stages of pregnancy may have developed physical dependence and may be at risk of developing a withdrawal syndrome in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

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. Clobazam must not be used in the first trimester of pregnancy and in women of childbearing potential not using contraception. In the later stages of pregnancy, it must only be used if there are compelling indications.

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 clobazam should be discontinued. If clobazam treatment is to be continued, use clobazam 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, clobazam must not be used in breast-feeding women. Neonates are generally more susceptible to the toxic effects of benzodiazepines.

4.7 Effects on ability to drive and use machines

Patients receiving clobazam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from clobazam therapy. Abilities may be impaired on the day following use.

4.8 Undesirable effects

The following side effects have been reported: dizziness, drowsiness, increased risk of fall, dry mouth, headache, nausea, constipation, loss of appetite and fine tremor of fingers, slowing of reaction time, ataxia, numbed emotions, muscle weakness and confusion.

Clobazam may cause sedation, leading to tiredness and sleepiness, especially at the beginning of treatment and when higher doses are used.

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Another possibility is the emergence of paradoxical reactions (e.g. restlessness, irritability, anxiety, suicidal tendencies, acute agitational states, aggressiveness, delusions, fits of rage, nightmares, hallucinations, psychotic reactions, frequent muscle spasms and insomnia including difficulty in falling asleep and/or sleeping through). In the event of such reactions, treatment with clobazam should be discontinued.

Anterograde amnesia, amnesia and memory impairment may occur even if benzodiazepines are used in the normal dose range but especially at higher dose levels. Amnestic effects may be associated with inappropriate behaviour. Pre-existing depression may be unmasked during benzodiazepine use.

Clobazam may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate.

After prolonged use of benzodiazepines, impairment of consciousness, sometimes combined with respiratory disorders, has been reported in very rare cases, particularly in elderly patients. It sometimes persists for some length of time.

There may be reversible abnormalities, such as disturbance in attention, disorders of articulation (slow or indistinct speech), visual disorders (e.g. diplopia, nystagmus), unsteadiness of gait and other motor functions, hypothermia, weight gain or loss of libido, especially in patients receiving high doses or long term treatment.

Cutaneous reactions, such as urticaria, pruritis, rash may develop in rare cases. Stevens-Johnson syndrome and Toxic Epidermal Necrolysis may occur including some cases with fatal outcomes. When used as an adjuvant in the treatment of epilepsy, this preparation may in rare cases cause restlessness and muscle weakness.

Tolerance and dependence may develop, especially with prolonged use.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <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.

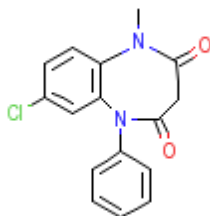
Treatment: In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken. Activated charcoal should be given to reduce absorption if the patient is conscious. Hypotension and respiratory depression should be managed according to general principles. Haemoperfusion, forced diuresis and 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.

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For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

Chemical Structure:



CAS Number: 22316-47-8

5.1 PHARMACODYNAMIC PROPERTIES

Clobazam is an anxiolytic and anticonvulsant of the benzodiazepine group.

Clobazam is the first anxiolytic medicine 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.

Site and Mode 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, dopamine, serotonin, acetylcholine, glycine and gamma-aminobutyric acid (GABA) as neurotransmitters may be involved in the mediation of the pharmacological effects.

Pharmacodynamics

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 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

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

Like the 1,4-benzodiazepines, clobazam 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 (clobazam: diazepam). Clobazam produces almost no muscular relaxation at normal dosage levels.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Clobazam is rapidly and completely absorbed from the gastrointestinal tract with peak plasma levels being achieved within two hours. The presence of food delays but does not affect the extent of absorption.

Distribution

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.

Biotransformation *The following information pertains to the oral solid dosage form:*

Clobazam is metabolised by demethylation, hydroxylation and methoxylation. Following oral administration, the serum contains unchanged clobazam with the chief metabolite being N-desmethyl-clobazam and smaller amounts of 4'-hydroxyclobazam and 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.

The following information pertains to the oral suspension dosage form:

The peak plasma level of clobazam after oral administration of Tapclob Oral Suspension 10 mg/5 ml was slightly higher than that observed after administration of a reference 10 mg tablet in a single dose, randomised, crossover bioequivalence study (mean C_{max} 267.5 ± 64.5 ng/mL and 220.4 ± 49.9 ng/mL, respectively).

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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 medicine and/or metabolites.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

In a carcinogenicity study, a significant increase in thyroid follicle cell adenoma was found in rats in the highest dose group (100 mg/kg body weight).

Clobazam – like other benzodiazepines – leads to activation of the thyroid in rats. These changes have not been observed in investigation in other species.

Genotoxicity

Clobazam had no known genotoxic or mutagenic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Xanthan Gum (E415)
Acesulfame Potassium (E950)
Raspberry Flavour
Sodium Propyl Hydroxybenzoate (E217)
Sodium Methyl Hydroxybenzoate (E219)
Disodium Hydrogen Phosphate Dihydrate (for pH-adjustment)
Sodium Dihydrogen Phosphate Dihydrate (for pH-adjustment)
Purified Water

6.2 Incompatibilities

N/A

6.3 Shelf life

2 years
28 days after first opening

6.4 Special precautions for storage

Do not store above 25°C

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6.5 Nature and contents of container

Amber glass bottles sealed with tamper evident, child-proof plastic screw caps.

The bottle is packed in a cardboard carton containing a 5ml syringe with an adaptor and a 30ml measuring cup along with the patient information leaflet.

Pack sizes: 150ml and 250 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This product may settle during storage. Please shake the bottle thoroughly before use.

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

7 MEDICINE SCHEDULE

Controlled Drug C5.

8 SPONSOR

Max Health Ltd, P O Box 65 231, Mairangi Bay, Auckland 0754

Ph:(09) 815 2664.

9 DATE OF FIRST APPROVAL

27 February 2020

10 DATE OF REVISION OF THE TEXT

27 February 2020

SUMMARY TABLE OF CHANGES

Date of Revision	Section Changed	Summary of new information