# New Zealand Data Sheet

## 1. ATIVAN 0.5 mg, 1.0 mg and 2.5 mg

Lorazepam tablets 0.5 mg, 1.0 mg and 2.5 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg, 1.0 mg or 2.5 mg of lorazepam
For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

0.5 mg: pale blue tablet, 4.8 mm round, flat, bevelled-edge, with '0.5' impressed on one side.

1 mg: flat, white to off white, round tablet with bevelled edges, bisected on one side and imprinted C11 on the other.

2.5 mg: flat, white to off white, round tablet with bevelled edges, bisected on one side and imprinted C18 on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ATIVAN (lorazepam) is indicated for:

1. Short-term treatment in adults:
   Moderate to severe anxiety or treatment of insomnia associated with anxiety.

   Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

2. Pre-medication before surgery in adults and children.

### 4.2 Dose and method of administration

ATIVAN is administered orally. For optimal results, dose, frequency of administration and duration of therapy should be individualised according to patient response. A short course of up to four weeks is recommended. The physician should periodically reassess the usefulness of the medication for the individual patient. Dosage should be individualised for maximum beneficial effect. In patients previously treated with anxiolytic agents, higher initial dosages of ATIVAN may be indicated.

***Adults***

The average daily dosage for treatment of anxiety is 2-3 mg administered in divided doses, however, this may range between 1 and 10 mg.

Dosages higher than 10 mg daily have been successfully employed in hospitalised cases, especially as adjunctive therapy in psychosis and severe depression.

For insomnia due to anxiety or transient situational stress, a single daily dose of 1-2 mg may be given, usually at bedtime.

For pre-surgical medication, a dosage of 2-4 mg of ATIVAN is recommended the night before surgery and/or 1-2 hours prior to the surgical procedure.

***Elderly or debilitated patients***

For elderly or debilitated patients, an initial dosage of 1 or 2 mg/day in divided doses is recommended, to be adjusted as needed and tolerated.

***Paediatric population***

The safety and effectiveness of lorazepam has not been established in children less than 16 years of age.

## 4.3 Contraindications

ATIVAN is contraindicated in:

- Patients with a known hypersensitivity to benzodiazepines or to any of the other ingredients.
- Patients with chronic obstructive airways disease with incipient respiratory failure.
- Acute pulmonary insufficiency: respiratory depression, sleep apnoea (risk of further respiratory depression).
- Obsessional states (inadequate evidence of safety and efficacy).
- Severe hepatic insufficiency (may precipitate encephalopathy).
- Myasthenia gravis.
- Monotherapy to treat depression or symptoms of anxiety associated with depression due to a risk of suicide (see section 4.4 special warnings and precautions for use).

## 4.4 Special warnings and precautions for use

***Duration of Treatment***

Benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of ATIVAN is not recommended.

Where long-term therapy is considered essential, the patient should be regularly reviewed.

### *Tolerance*

There is evidence that tolerance develops to the sedative effects of benzodiazepines. Tolerance as defined by a need to increase the dose in order to achieve the same therapeutic effect seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to benzodiazepines may develop from continued therapy. Tolerance to sedation may occur with benzodiazepines especially in those with drug seeking behaviour.

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).

### *Hypotension*

Although hypotension has occurred only rarely, ATIVAN should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

### *Glaucoma*

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

### *Impaired Renal/Liver Function and Blood Dyscrasias*

Patients with impaired renal or hepatic function should be monitored frequently and have their dosage adjusted carefully according to patient response. Lower doses may be sufficient in these patients.

As with all CNS-depressants, the use of benzodiazepines may precipitate encephalopathy in patients with severe hepatic insufficiency. Therefore, use in these patients is contraindicated.

Some patients have developed blood dyscrasias, and some have had elevations of liver enzymes. Periodic haematology and liver function assessments are recommended where repeated courses of treatment are considered clinically necessary.

### *Depression, Psychosis and Schizophrenia*

ATIVAN is not intended for the primary treatment of psychotic illness or depressive disorders. It must not be used alone to treat depression or symptoms of anxiety associated with depression due to a risk of suicide.

Pre-existing depression may emerge during benzodiazepine use. Benzodiazepines may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal.

The use of benzodiazepines may have a disinhibiting effect and may uncover suicidal tendencies in depressed patients. Therefore, benzodiazepines should be used with caution and the prescription quantity should be limited in these patients.

### *Psychiatric and/or paradoxical reactions*

As with other benzodiazepines and CNS active drugs, three idiosyncratic symptom clusters, which may overlap, have been described.

- Amnestic symptoms: anterograde amnesia with appropriate or

inappropriate behavior;

- Confusional states: disorientation, derealisation, depersonalization and/or clouding of consciousness; and
- Agitational states: sleep disturbances, restlessness, irritability, aggression and excitation.

Lorazepam should be discontinued if confusion or agitation occurs.

Paradoxical reactions such as acute rage, stimulation or excitement may occur. Such reactions may be more likely to occur in children and the elderly. Should such reactions occur, ATIVAN should be discontinued.

***Memory impairment***

Transient anterograde amnesia or memory impairment has been reported in association with the use of benzodiazepines. This effect may be advantageous when lorazepam is used as a premedicant. However, if lorazepam is used for insomnia due to anxiety, patients should ensure that they will be able to have a period of uninterrupted sleep which is sufficient to allow dissipation of drug effect (e.g. 7-8 hours).

***Elderly patients***

Lorazepam should be used with caution in the elderly due to the risk of sedation and/or musculoskeletal weakness that can increase the risk of falls with serious consequences in this population.

Lower doses should be used in elderly patients (see section 4.2 Dose and method of administration).

***Epilepsy***

Abrupt withdrawal of benzodiazepines in patients with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

***Abuse***

Abuse of benzodiazepines has been reported. Benzodiazepines should be used in caution in patients with a history of alcohol or drug abuse, dependence on CNS depressants, those 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.

Before prescribing and throughout treatment, assess each patient’s risk for abuse, misuse, and addiction. Use of benzodiazepines, particularly patients at elevated risk, necessitates counselling about the risks and proper use.

***Dependence and withdrawal***

The use of benzodiazepines may lead to dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. The risk of dependence increases with dose and duration of treatment, and in patients with a history of alcoholism and/or drug abuse, or in patients with marked personality disorders. Regular monitoring in such patients is essential.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation. These symptoms can

range from insomnia, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (eg 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 states, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in those patients who have received excessive doses over a prolonged period or in patients who have been dependent on alcohol or other narcotic drugs in the past. Accordingly, ATIVAN should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. An individualized withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from four weeks to four months have been suggested. 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 and anxiety 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 taken for relatively short periods.

***Concomitant use with alcohol/CNS depressants***

The concomitant use of lorazepam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of lorazepam which may include severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5 Interaction with other medicines and other forms of interaction).

***Risks from Concomitant Use with Opioids***

Concomitant use of benzodiazepines, including lorazepam, 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 drug-related mortality compared to use of opioids alone. If a decision is made to prescribe ATIVAN 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 ATIVAN is used with opioids (see section 4.5 Interaction with other medicines and other forms of interaction).

***Paediatric Use***

The safety and effectiveness of lorazepam has not been established in children less than 16 years of age.

### *Paediatric neurotoxicity*

Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans. Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also section 4.6).

### *Effects on laboratory tests*

No interference with laboratory tests have been identified or reported with the use of lorazepam.

## 4.5 Interaction with other medicines and other forms of interaction

### *CNS depressants*

The benzodiazepines, including ATIVAN, 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, sedating antihistamines or narcotic analgesics and anaesthetics.

### *Opioids*

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA 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.

### *Cytochrome P450 substrates*

The cytochrome P450 system has not been shown to be involved in the disposition of ATIVAN and, unlike many benzodiazepines, pharmacokinetic interactions involving the P450 system have not been observed with ATIVAN.

### *Medicines with anticholinergic effects*

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

### *Clozapine*

There have been reports of marked sedation, excessive salivation, and ataxia when lorazepam and clozapine have been given concomitantly.

### *Antiepileptics*

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, and that serum level monitoring of the anticonvulsant be performed more frequently.

### *Theophylline/aminophylline*

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including lorazepam.

## 4.6 Fertility, pregnancy and lactation

### *Women of childbearing potential*

Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy. When treating women of childbearing potential, the benefits of treatment should be weighed against the risks and the patient should be informed of the increased risk of miscarriage.

If lorazepam is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the medicine if she intends to become or suspects that she is pregnant.

### *Use in Pregnancy*

Category C.

Benzodiazepines should not be used during pregnancy, especially during the first and last trimesters. Benzodiazepines may cause fetal damage when administered to pregnant women. Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy.

Infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence. Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnoea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.

Neonates appear to conjugate lorazepam slowly, the glucuronide being detectable in the urine for more than seven days. Glucuronidation of lorazepam

may competitively inhibit the conjugation of bilirubin, leading to hyperbilirubinaemia in the newborn.

*Risk summary statement*

Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

*Preclinical data*

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

***Use During Lactation***

Caution should be exercised when ATIVAN is given to breast feeding women. ATIVAN is excreted in human breast milk and may cause drowsiness and feeding difficulties in the infant.

***Effects on fertility***

A pre-implantation study in rats was performed with oral lorazepam at a 20 mg/kg dose which showed no impairment of fertility.

## 4.7 Effects on ability to drive and use machines

Patients should be advised that sedation, amnesia, impaired concentration, dizziness, blurred vision and impaired muscular function may occur and that, if affected, they should not drive or use machines, or take part in other activities where this would put themselves or others at risk. Abilities may be impaired on the day following use particularly with insufficient sleep. Concurrent medicines may increase these effects (see section 4.5 Interaction with other medicines and other forms of interaction).

## 4.8 Undesirable effects

Adverse reactions, if they occur, are usually observed at the beginning of therapy and generally decrease in severity or disappear with continued use or upon decreasing the dose.

Most frequently reported adverse reactions associated with benzodiazepines include daytime drowsiness, dizziness, muscle weakness, and ataxia.

Adverse reactions are listed by frequency: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000; Very rare (<1/10,000); not known (cannot be estimated from the available data

<u>Blood and lymphatic system disorders</u>

Very rare: Thrombocytopenia, leucopenia, agranulocytosis, pancytopenia

Immune system disorders

Very rare: Hypersensitivity including anaphylaxis/anaphylactoid reactions

Endocrine disorders

Very rare: Inappropriate antidiuretic hormone secretion, hyponatraemia

Psychiatric disorders

Rare: Confusion, depression and unmasking of depression, numbed emotions, disinhibition, euphoria, appetite changes, sleep disturbance, change in libido, decreased orgasm.

Unknown: Dependence, suicidal ideation/attempt

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, insomnia, nightmares, hallucinations, psychoses, sexual arousal, and inappropriate behaviour have been occasionally reported during use.

Nervous system disorders

Very common: Daytime drowsiness, sedation

Common: Dizziness, ataxia

Rare: headache, reduced alertness, dysathria/slurred speech, transient anterograde amnesia or memory impairment.

Very rare: Tremor, extrapyramidal reactions, coma (see section 4.9 overdose)

Eye disorders

Rare: Visual disturbances (diplopia, blurred vision)

Vascular disorders

Rare: Hypotension (see section 4.4 special warnings and precautions for use)

Respiratory, thoracic and mediastinal disorders:

Rare: Apnoea, worsening of sleep apnoea, worsening of obstructive pulmonary disease. Respiratory depression (see section 4.9 overdose).

Gastrointestinal disorders

Rare: Nausea, constipation, salivation changes

Hepatobiliary disorders

Rare: Abnormal liver function test values (increases in bilirubin, transaminases, alkaline phosphatase), jaundice

Skin and subcutaneous tissue disorders

Rare: Rash, allergic dermatitis

Musculoskeletal disorders

Common: Muscle weakness

Reproductive system and breast disorders

Rare: Impotence

General disorders

Common: Asthenia, fatigue

Very rare: Hypothermia

Injury, poisoning and procedural complications

Not known: Fall

***Reporting of suspected adverse reactions***

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://pophealth.my.site.com/carmreportnz/s/.

### 4.9 Overdose

***Symptoms***

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 proves fatal.

***Treatment***

In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken.

Treatment of overdose is supportive and symptomatic. If an overdose of oral benzodiazepines occurred within the last 1-2 hours, consider activated charcoal which may reduce absorption. In patients who are not fully conscious or who have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube once the airway is protected. Hypotension and respiratory depression should be managed according to general principles.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be used in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

The exact mechanism of action of benzodiazepines has not yet been elucidated, however, benzodiazepines appear to work through several mechanisms. Benzodiazepines presumably exert their effects by binding to specific receptors at several sites within the central nervous system either by potentiating the effects of synaptic or pre-synaptic inhibition mediated by gamma-aminobutyric acid or by directly affecting the action potential generating mechanisms.

Pharmacokinetic properties

ATIVAN is readily absorbed when given orally. Peak concentrations in plasma occur approximately 2 hours following administration. The half-life of ATIVAN in human plasma is approximately 12-16 hours. At clinically relevant concentrations, ATIVAN is approximately 90% bound to plasma proteins.

Lorazepam is metabolised in the liver, mainly to the inactive glucuronide of lorazepam. Seventy to seventy-five per cent of the dose is excreted as the glucuronide in the urine. The glucuronides of lorazepam have no demonstrable CNS activities in animals, and there are no active metabolites of ATIVAN.

The plasma levels of ATIVAN are proportional to the dose given. There is no evidence of excessive accumulation of ATIVAN on administration up to 6 months nor is there any indication of induction of drug-metabolising enzyme under these conditions. ATIVAN is not a substrate for N-dealkylating enzymes of the cytochrome P450 system nor is it hydroxylated to any significant extent.

Studies comparing young and elderly subjects have shown that the pharmacokinetics of ATIVAN remain unaltered with advancing age. No changes in absorption, distribution, metabolism and excretion were reported in patients with hepatic disease (hepatitis, alcoholic cirrhosis). As with other benzodiazepines, the pharmacokinetics of lorazepam may change in patients with impaired renal function and the medication should be used with caution.

## 5.2 Preclinical safety data

### *Animal toxicology and/or pharmacology*

Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

***Carcinogenesis and Mutagenesis***

No evidence of carcinogenic potential emerged in rats or mice during an 18-month study with oral lorazepam. An investigation of the mutagenic activity of lorazepam on Drosophila melanogaster indicated that it was mutationally inactive.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, magnesium stearate and polacrillin potassium, indigo carmine (0.5mg only).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

0.5 mg: 48 months
1 mg: 20 months
2 mg: 24 months

### 6.4 Special precautions for storage

Store below 25°C. Protect from light.

### 6.5 Nature and contents of container

0.5 mg: glass bottles of 100s and 250s (both not marketed).

1 mg: glass bottles of 50s and 250s

2.5 mg: glass bottles of 50s and 100s

### 6.6 Special precautions for disposal

Not applicable.

## 7. MEDICINE SCHEDULE

CONTROLLED DRUG C5

## 8. SPONSOR

Pharmacy Retailing (NZ) Limited
Trading as Healthcare Logistics
58 Richard Pearse Drive

Airport Oaks

Auckland, New Zealand
Telephone (09) 9185 100

Email: aspen@aspenpharma.co.nz

## 9. DATE OF FIRST APPROVAL

14 February 1974

## 10. DATE OF REVISION OF THE TEXT

3 February 2025

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 4.4 | At the request of Medsafe, additional safety information regarding risks of misuse, addiction, dependence and withdrawal reactions. |
| 3 | Updated tablet appearance |
| 6.1 | Change to excipients |
| 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9 | Addition of safety information as per Medsafe request including benzodiazepines and the risk of miscarriage. |