ECENTOPAM Plus

1. Composition

Escitalopram 10mg

Clonazepam 0.5mg

2. Dosage form and strength

Ecentopam tablets are available in pack of 10 tablets.

3. Clinical particulars

3.1 Therapeutic indication

Ecentopam is used in treatment of Major Depression Disorder (MDD) and mixed anxiety disorder

3.2 Posology and method of administration

Recommended oral dose of Ecentopam is one tablet once a day.

3.3 Contraindication

Ecentopam is contraindicated in case of:

- Hypersensitivity for any component
- Treatment with Monoamine Oxidase Inhibitors (MAOIs)
- Liver disease
- Acute angle Glaucoma
- Pregnancy and breast feeding

3.4 Special warnings and precautions for use

- Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression. It should be noted that Ecentopam Tablets is not approved for use in treating bipolar depression.
- Ecentopam Tablets should be used cautiously in patients with a history of mania and should be discontinued in any patient entering the manic phase.
- The concomitant use of Ecentopam Tablets with MAOIs intended to treat depression is contraindicated. If concomitant treatment of Ecentopam Tablets with a 5-

hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

- The concomitant use of Ecentopam Tablets with serotonin precursors (such as tryptophan) is not recommended. Treatment with Ecentopam Tablets and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.
- Ecentopam Tablets should be discontinued if a patient develops seizures for the first time, or if there is an increase in seizure frequency (in patients with a previous diagnosis of epilepsy). SSRIs should be avoided in patients with unstable epilepsy, and patients with controlled epilepsy should be closely monitored.
- Discontinuation of Ecentopam Tablets should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.
- Patients should be cautioned about the risk of bleeding associated with the concomitant use of Ecentopam Tablets and NSAIDs, aspirin, or other drugs that affect coagulation. Caution is advised in patients taking Ecentopam Tablets, particularly in concomitant use with oral anticoagulants.
- Patients should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during Ecentopam Tablets therapy.
- In patients with diabetes, treatment with an SSRI may alter glycaemic control (hypoglycaemia or hyperglycaemia). Insulin and/or oral hypoglycaemic dosage may need to be adjusted when given concomitantly with Ecentopam Tablets.
- Caution is advisable in using Ecentopam Tablets in patients with diseases or conditions that produce altered metabolism or hemodynamic responses e.g. coronary heart disease. Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease.
- Clonazepam may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, Ecentopam Tablets should be used with caution in patients with chronic respiratory diseases.
- The dosage of Ecentopam Tablets must be carefully adjusted to individual requirements in patients with pre-existing disease of the respiratory system (e.g. chronic obstructive pulmonary disease).
- The abrupt withdrawal of clonazepam, particularly in those patients with epilepsy on long-term, high-dose therapy, may precipitate status epilepticus.

3.5 Drug interactions

- Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs including escitalopram and the potential for serotonin syndrome, caution is advised when Ecentopam Tablets are co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol or St. John's Wort. The concomitant use of Ecentopam Tablets with other SSRIs, SNRIs or tryptophan is not recommended.

- Triptans

There has been rare post marketing reports of serotonin syndrome with use of an SSRI and a triptans. Concomitant treatment of Ecentopam Tablets with a triptans is clinically warranted; careful observation of the patient is advised, particularly during treatment initiation and dose increases.

- CNS Drugs

Given the primary CNS effects of escitalopram and clonazepam, caution should be used when Ecentopam Tablets is taken in combination with other centrally acting drugs.

The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, anti-anxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs. The dose of Ecentopam Tablets must be carefully adjusted in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents.

Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine, or Phenobarbital. The effect of clonazepam on the metabolism of other drugs has not been investigated.

- Alcohol

Although escitalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Ecentopam Tablets is not recommended. In combination with clonazepam, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects. Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse. Patients should be advised to avoid alcohol while taking Ecentopam Tablets.

- Monoamine Oxidase Inhibitors (MAOIs)

Irreversible non-selective MAOIs

Cases of serious reactions have been reported in patients receiving an SSRI in combination with a non-selective, irreversible MAOI and in patients who have recently discontinued SSRI treatment and have been started on such MAOI treatment. In some cases, the patient developed serotonin syndrome.

Ecentopam Tablets is contra-indicated in combination with non-selective, irreversible MAOIs. Ecentopam Tablets may be started 14 days after discontinuing treatment with an irreversible MAOI. At least 7 days should elapse after discontinuing escitalopram treatment, before starting a non-selective, irreversible MAOI.

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of Ecentopam Tablets with a MAO-A inhibitor such as moclobemide is contraindicated.

Reversible, non-selective MAO-inhibitor (linezolid)

The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with Ecentopam Tablets.

Irreversible, selective MAO-B inhibitor (selegiline)

In combination with selegiline (irreversible MAO-B inhibitor), caution is required due to the risk of developing serotonin syndrome. Selegiline doses up to 10 mg/day have been safely co-administered with racemic citalopram.

- Drugs that Interfere with Haemostasis (NSAIDs, Aspirin, Warfarin, etc.)

Serotonin release by platelets plays an important role in haemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Ecentopam Tablets is initiated or discontinued.

- Cimetidine

In subjects who had received 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine resulted in an increase in citalopram AUC and Cmax of 43% and 39%, respectively. The clinical significance of these findings is unknown. Cimetidine (known

inhibitor of hepatic enzymes), has shown to reduce the clearance of benzodiazepines and may potentiate their action. Caution must be exercised if cimetidine and Ecentopam Tablets are used concomitantly.

- Digoxin

In subjects who had received 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

- Lithium

Co-administration of racemic citalopram (40 mg/day) and lithium (30 mmol/day) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Ecentopam Tablets and lithium are co-administered.

- Pimozide and Citalopram

In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec, compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or Cmax of pimozide. The mechanism of this pharmacodynamic interaction is not known.

- Sumatriptan

There have been rare postmarketing reports describing patients with weakness, hyper-reflexia and in coordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and Ecentopam Tablets is clinically warranted, appropriate observation of the patient is advised.

- Theophylline

Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

- Carbamazepine

Combined administration of racemic citalopram (40 mg/day for 21 days) and carbamazepine (titrated to 400 mg/day) did not significantly affect the pharmacokinetics of carbamazepine,

a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered, if Ecentopam Tablets and carbamazepine are co-administered.

- Triazolam

Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

- Ketoconazole

Combined administration of racemic citalopram 40 mg and ketoconazole 200 mg, a potent CYP3A4 inhibitor, decreased the Cmax and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

- Ritonavir

Combined administration of a single dose of ritonavir 600 mg, both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram 20 mg did not affect the pharmacokinetics of ritonavir.

- CYP3A4 and CYP2C19 Inhibitors

In vitro studies indicated that CYP3A4 and CYP2C19 are the primary enzymes involved in the metabolism of escitalopram. However, co-administration of escitalopram 20 mg and ritonavir 600 mg, a potent inhibitor of CYP3A4 and CYP2C19, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

Co-administration of escitalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram. Thus, caution should be exercised when Ecentopam Tablets is used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine).

Although clinical studies have not been performed, based on the involvement of the cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme system, notably oral antifungal agents, should be used cautiously in patients receiving clonazepam.

- Cytochrome P-450 inducers

Cytochrome P-450 inducers, such as phenytoin, carbamazepine and phenobarbital, induce clonazepam metabolism, causing an approximately 30% decrease in plasma clonazepam levels. Known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.

- Drugs Metabolized by Cytochrome P4502D6

In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited in vivo data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in Cmax and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

- Metoprolol

Administration of 20 mg/day escitalopram for 21 days in healthy volunteers resulted in a 50% increase in Cmax and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Co-administration of Ecentopam Tablets and metoprolol had no clinically significant effects on blood pressure or heart rate.

- St. John´s Wort

Concomitant use of SSRIs and herbal remedies containing St. John´s Wort (Hypericum perforatum) may result in an increased incidence of adverse reactions.

- Medicinal Products Lowering the Seizure Threshold

SSRIs can lower the seizure threshold. Caution is advised when concomitantly using Ecentopam Tablets and other medicinal products capable of lowering the seizure threshold e.g., antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol.

- Ranitidine

Literature reports suggest that ranitidine, an agent that decreases stomach acidity, does not greatly alter clonazepam pharmacokinetics. In a study in which the 2 mg clonazepam orally disintegrating tablet was administered with and without propantheline (an anticholinergic agent with multiple effects on the GI tract) to healthy volunteers, the AUC of clonazepam

was 10% lower and the Cmax of clonazepam was 20% lower when the orally disintegrating tablet was given with propantheline compared to when it was given alone.

- Antiepileptic Drugs

When Clonazepam is used in conjunction with other antiepileptic drugs, side-effects such as sedation and apathy, and toxicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment. The combination of clonazepam and sodium valproate has, rarely, been associated with the development of absence status epilepticus. Although some patients tolerate and benefit from this combination of drugs, this potential hazard should be borne in mind when its use is considered.

3.6 Use in special population

- Pediatric: Ecentopam Tablets should not be used in the treatment of children and adolescents below the age of 18 years. Safety and effectiveness of Ecentopam Tablets has not been established in children and adolescents below the age of 18 years.
- Geriatric: Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Ecentopam Tablets and observed closely.
- Liver impairment: In patients with severe liver damage (e.g. cirrhosis of the liver), particular caution needs to be taken.
- Renal failure: In patients with severe renal impairment, treatment with Ecentopam Tablets should be done with caution.
- Pregnancy and lactation: Ecentopam Tablets should not be used in pregnancy unless clearly necessary. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Ecentopam Tablets are administered to a lactating mother.

3.7 Effects on ability to drive and use machine

Since clonazepam produces CNS depression, patients receiving Ecentopam Tablets should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle.

3.8 Undesirable effects

The most common set of undesirable effects observed are dry mouth, increased sweating, headache, par aesthesia, dizziness, nausea, diarrhoea, constipation, indigestion, abdominal pain, vomiting, flatulence, influenza-like symptoms, fatigue, abnormal dreaming, lethargy, insomnia, somnolence, decreased appetite, decreased libido, yawning, rhinitis, sinusitis, ejaculation disorder, impotence, anorgasmia and menstrual disorders.

3.9 Overdose

Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, include escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor, and agitation to rare cases of serotonin syndrome, convulsion, and coma), gastrointestinal system (nausea, vomiting) and the cardiovascular system (hypotension, tachycardia, QT prolongation, arrhythmia, and very rare cases of torsade de pointes) and electrolyte/fluid balance conditions (hypokalaemia, hyponatraemia) and sleep disturbances (insomnia somnolence). Acute renal failure has been very rarely reported accompanying overdose. In case of clonazepam, symptoms of overdosages are like those produced by other CNS depressants i.e., somnolence, confusion, coma and diminished reflexes.

Management of overdose includes establishing and maintaining an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Gastric lavage should be carried out as soon as possible after oral ingestion. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control centre for additional information on the treatment of any overdose.

There is no specific antidote for escitalopram overdosage. However clonazepam being a benzodiazepine, flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

Flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures. Serious sequelae are rare unless other drugs or alcohol have been taken concomitantly.

4. Pharmacological properties

4.1 Mechanism of action

The mechanism of the antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to the potentiation of serotonergic activity in the central nervous system (CNS), resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

The precise mechanism by which clonazepam exerts its anxiolytic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.

4.2 Pharmacodynamic properties

In vitro and in vivo studies suggests that escitalopram is a highly selective serotonin (5-HT) reuptake inhibitor (SSRI) with a high affinity for the primary binding site, and has minimal effects on norepinephrine and dopamine neuronal reuptake. It also binds to an allosteric site on the serotonin transporter, with a 1,000-fold lower affinity. Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to the inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic (5-HT1–7)or other receptors including alpha- and beta-adrenergic, dopamine (D1–5), histamine (H1–3), muscarinic (M1–5), benzodiazepine and opiod receptors. Escitalopram also does not bind to or has low affinity for various ion channels, including Sodium (Na+), Potassium (K+), Chloride (Cl–) and Calcium (Ca++) channels. Antagonism of the muscarinic, histaminergic and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular side effects of other psychotropic drugs.

4.3 Pharmacokinetic properties

- Escitalopram

<u>Absorption</u>

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day.

Absorption is almost complete and independent of food intake (mean time to maximum concentration is 4 hours after multiple dosing). As with racemic citalopram, the absolute bio-availability of escitalopram is expected to be about 80%. Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours.

<u>Distribution</u>

The binding of escitalopram to human plasma proteins is approximately 56%. The apparent volume of distribution (Vd,β/F) after oral administration is about 12–26 L/kg. At the steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2–2.5 times the plasma concentrations observed after a single dose.

Metabolism

Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27–32 hours. Escitalopram is metabolized to S-demethylcitalopram (S-DCT) and S-didemethylcitalopram (S-DDCT). Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidized to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. After multiple dosing, the mean concentrations of the demethyl and didemethyl metabolites are usually 28–31% and <5%, respectively, of the escitalopram concentration. In humans, unchanged escitalopram is the predominant compound in plasma. At the steady state, the concentration of the escitalopram metabolite, S-DCT, in plasma is approximately one-third that of escitalopram.

In vitro studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic (5-HT1–7) or other receptors, including alpha- and beta-adrenergic, dopamine (D1–5), histamine (H1–3), muscarinic (M1–5) and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels, including Na+, K+, Cl– and Ca++ channels. In vitro studies using human liver microsomes indicated that cytochrome (CY) P3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram. Some contribution by the enzymes, CYP3A4 and CYP2D6, is also possible.

Elimination

The elimination half-life (t½β) after multiple dosing is about 30 hours and the oral plasma clearance (Cloral) is about 0.6 L/min. Following oral administration of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-DCT is about 8% and 10%, respectively. The major metabolites have a significantly longer half-life. Escitalopram and its major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.

With once-daily dosing, steady-state plasma concentrations are achieved within approximately 1 week. Average steady-state concentrations of 50 nmol/L (range: 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

- Clonazepam

Absorption

Clonazepam is rapidly and completely absorbed after oral administration. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. Bioavailability is 90% after oral administration. Routine monitoring of plasma concentrations of clonazepam is of unproven value since this does not appear to correlate well with either therapeutic response or side-effects.

Distribution

The mean volume of distribution of clonazepam is estimated at about 3 L/kg. Clonazepam must be assumed to cross the placental barrier and has been detected in maternal milk.

Metabolism

The biotransformation of clonazepam involves oxidative hydroxylation and reduction of the 7-nitro group by the liver with formation of 7-amino or 7-acetylamino compounds, with trace amounts of 3-hydroxy derivatives of all three compounds, and their glucuronide and sulphate conjugates. The nitro compounds are pharmacologically active, whereas the amino compounds are not.

Within 4 - 10 days 50 - 70% of the total radioactivity of a radiolabelled oral dose of clonazepam is excreted in the urine and 10 - 30% in the faeces, almost exclusively in the form of free or conjugated metabolites. Less than 0.5% appears as unchanged clonazepam in the urine.

Elimination

The elimination half-life is between 20 and 60 hours (mean 30 hours).

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

24 months.

7.3 Storage and handling instructions

Store in a cool dry place. Keep away from light