Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

Brand Name : ZEPIN SYRUP **Generic Name :** Carbamazepine Syrup 100 mg/5 ml	2021
Module 1 Administrative Information and Product Information **1.5** Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

ZEPIN SYRUP (Carbamazepine Syrup 100 mg / 5 ml)

2. Qualitative and Quantitative Composition:

Each 5 ml contains: Carbamazepine BP 100 mg

3. Pharmaceutical form:

Yellowish Coloured Syrup

4. Clinical particulars:

4.1 Therapeutic indications

Carbamazepine is indicated for

- epilepsy (generalised tonic-clonic and partial seizures)

Note: Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences.

- the paroxysmal pain of trigeminal neuralgia

- the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

4.2 Posology and method of administration

Posology

Since a given dose of carbamazepine oral suspension will produce higher peak levels than the same dose in tablet form, it is advisable to start with low doses of the liquid and to increase them slowly so as to avoid adverse effects on the central nervous system such as dizziness and lethargy.

When switching a patient from tablets to liquid the same overall dose may be used but in smaller, more frequent, doses.

Before deciding to initiate treatment, patients of Han Chinese and Thai origin should whenever possible be screened for HLA-B*1502 as this allele strongly predicts the risk of severe carbamazepine-associated Stevens-Johnson syndrome (see information on genetic testings and cutaneous reactions in section 4.4).

Epilepsy

The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/ml (17 to 50 micromoles/litre) (see warnings and precautions).

Adults

It is advised that with all formulations of carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.

Carbamazepine should be taken in a number of divided doses although initially 100-200 mg once to twice daily is recommended. This may be followed by a slow increase until the best response is obtained, often 800-1200 mg daily. In some instances, 1600 mg or even 2000 mg daily may be necessary.

Elderly

Due to the potential for drug interactions, the dosage of carbamazepine should be selected with caution in elderly patients.

Paediatric population

It is advised that with all formulations of carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.

Usual dosage 10-20 mg/kg bodyweight daily in several divided doses.

Age up to 1 year:	100 to 200 mg daily (5-10 ml liquid per day)
1-5 years:	200 to 400 mg daily (10-20 ml liquid per day)
5-10 years:	400 to 600 mg daily (20-30 ml liquid per day to be taken in divided doses)
10-15 years:	600 to 1000 mg daily (30-50 ml liquid per day to be taken in several divided doses)
15 years of age:	800 to 1200 mg daily (same as adult dose).

Maximum recommended dose

Up to 6 years of age:	35 mg/kg/day
6-15 years of age:	1000 mg/day
>15 years of age:	1200 mg/day.

Wherever possible anti-epileptic agents should be prescribed as the sole drug anti-epileptic agent but if used in polytherapy, the same incremental dosage pattern is advised.

When carbamazepine is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the dosage of the other antiepileptic(s) (see 4.5 Interaction with other medicinal products and other forms of interaction).

Trigeminal neuralgia

Slowly raise the initial dosage of 200-400 mg daily until freedom from pain is achieved (normally at 200 mg 3-4 times daily). In the majority of patients a dosage of 200 mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, doses of 1600 mg carbamazepine daily may be needed. However, once the pain is in remission, the dosage should be gradually reduced to the lowest

possible maintenance level. Maximum recommended dose is 1200 mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

Elderly

Dosage in Trigeminal neuralgia

Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of carbamazepine should be selected with caution in elderly patients.

In elderly patients, an initial dose of 100 mg twice daily is recommended. The initial dosage of 100 mg twice daily should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200 mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

For the prophylaxis of manic depressive psychosis in patients unresponsive to lithium therapy

Initial starting dose of 400 mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600 mg given in divided doses is reached. The usual dosage range is 400-600 mg daily, given in divided doses.

Special populations

Renal impairment / Hepatic impairment

No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

Method of administration

Carbamazepine oral suspension is given orally, usually in two or three divided doses. Carbamazepine oral suspension (oral suspension should be shaken before use) may be taken during, after or between meals.

4.3 Contraindications

- known hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any of the excipients listed in section 6.1

- patients with atrioventricular block, a history of bone marrow depression or a history of hepatic porphyria (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda)

- the use of carbamazepine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs) (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Warnings

Agranulocytosis and aplastic anaemia have been associated with carbamazepine; however, due to the very low incidence of these conditions, meaningful risk estimates for carbamazepine are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anaemia.

Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of carbamazepine. Nonetheless, complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline, and periodically thereafter.

Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult his physician immediately.

If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored (see section 4.8 Undesirable effects). However, treatment with carbamazepine should be discontinued if the patient develops leukopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Carbamazepine should also be discontinued if any evidence of significant bone marrow depression appears.

Liver function tests should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease.

Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase. This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the withdrawal of carbamazepine.

Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with carbamazepine suspended pending the outcome of the evaluation.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for carbamazepine.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN: also known as Lyell's syndrome) have been reported very rarely with carbamazepine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, carbamazepine should be withdrawn at once and alternative therapy should be considered.

Cutaneous reactions

Serious and sometimes fatal cutaneous reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carbamazepine. These reactions are estimated to occur in 1-6 per 10 000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher.

There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions (see section 4.2).

Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

HLA-B*1502 allele – in Han Chinese, Thai and other Asian populations

HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine (see section 4.2). If these individuals test positive, carbamazepine should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still very rarely occur.

There are some data that suggest an increased risk of serious carbamazepine-associated TEN/SJS in other Asian populations. Because of the prevalence of this allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered.

The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (< 1%).

HLA-A*3101 allele - European descent and Japanese populations

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash (see section 4.8) in people of European descent and the Japanese.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population.

The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of Northern European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.

There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine treatment.

If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed risks.

Other dermatologic reactions

Mild skin reactions e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing the drug should the reaction worsen with continued use.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption).

Hypersensitivity

Carbamazepine may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), reactivation of HHV6 associated with DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various

combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon) see section 4.8 Undesirable Effects.

In general, if signs and symptoms suggestive of hypersensitivity reactions occur, carbamazepine should be withdrawn immediately.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that 25-30% of these patients may experience hypersensitivity reactions with oxacarbazepine (Trileptal).

Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone and phenobarbital).

Carbamazepine should be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, carbamazepine may exacerbate seizures. In case of exacerbation of seizures, carbamazepine should be discontinued.

An increase in seizure frequency may occur during switchover from an oral formulation to suppositories.

Dose reduction and withdrawal effects

Abrupt withdrawal of carbamazepine may precipitate seizures therefore carbamazepine withdrawal should be gradual. If treatment with carbamazepine has to be withdrawn abruptly in a patient with epilepsy, the changeover to another anti-epileptic drug should if necessary be effected under the cover of a suitable drug.

Pregnancy and females of reproductive potential

Carbamazepine may be associated with foetal harm when administered to a pregnant woman (see section 4.6 Fertility, pregnancy and lactation). Carbamazepine SUN should be used during pregnancy only if the potential benefit justifies the potential risks.

Adequate counselling should be made available to all pregnant women and women of childbearing potential, regarding the risks associated with pregnancy due to potential teratogenic risk to the foetus (see section 4.6 Fertility, pregnancy and lactation).

Women of childbearing potential should use effective contraception unaffected by enzyme inducing drugs, during treatment with Carbamazepine SUN and for a period of 28 days after discontinuation of treatment (see section 4.6 Fertility, pregnancy and lactation).

Endocrinological effects

Breakthrough bleeding has been reported in women taking carbamazepine while using hormonal contraceptives. The reliability of hormonal contraceptives may be adversely affected by carbamazepine and women of childbearing potential should be advised to consider using alternative forms of birth control while taking carbamazepine.

Patients taking carbamazepine and requiring hormonal contraception should receive a preparation containing not less than 50 µg oestrogen or use of some alternative non-hormonal method of contraception should be considered.

Monitoring of plasma levels

Although correlations between dosages and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following conditions: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used (see 4.5 Interaction with other medicinal products and other forms of Interaction).

Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

Precautions

Carbamazepine should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with carbamazepine.

Baseline and periodic complete urinalysis and BUN determinations are recommended.

Hyponatremia

Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If hyponatraemia is observed, water restriction is an important counter-measurement if clinically indicated.

Hypothyroidism

Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism. Hence thyroid function monitoring is suggested to adjust the dosage of thyroid replacement therapy.

Anticholinergic effects

Carbamazepine has shown mild anticholinergic activity; patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy (see section 4.8).

Psychiatric effects

The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

Interactions

Co-administration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with carbamazepine can induce adverse reactions (increase of carbamazepine or carbamazepine-10,11 epoxide plasma concentrations respectively). The dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored.

Co-administration of CYP3A4 inducers with carbamazepine may decrease carbamazepine plasma concentrations and its therapeutic effect, while discontinuation of a CYP3A4 inducer may increase carbamazepine plasma concentrations. The dosage of carbamazepine may have to be adjusted.

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism. See section 4.5 Interactions.

Female patients of childbearing potential should be warned that the concurrent use of carbamazepine with hormonal contraceptives may render this type of contraceptive ineffective (see sections 4.5 Interactions and 4.6 Pregnancy and lactation). Alternative non-hormonal forms of contraception are recommended when using carbamazepine.

Falls

Carbamazepine treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see section 4.8 Undesirable effects) which may lead to falls and,

consequently fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete risk assessment of fall should be considered recurrently for patients on long-term carbamazepine treatment.

This medicinal product contains the colouring orange yellow S. It may cause allergic reactions.

This medicinal product contains sorbitol (E420). Each 5 ml of suspension contains 2.8 g of sorbitol, which is equivalent to 0.56 g/ml. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

This medicinal product contains propylene glycol. Each 5 ml of suspension contains 250 mg of propylene glycol, which is equivalent to 50 mg/ml.

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

This medicinal product contains potassium sorbate. Each 5 ml of suspension contains less than 1 mmol (39 mg) of potassium, i.e. essentially “potassium free”.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P4503A4 (CYP3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine 10, 11-epoxide. Co-administration of inhibitors of CYP3A4 may result in increased plasma concentrations which could induce adverse reactions. Co-administration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to potential decreases in the carbamazepine serum level and therapeutic effect.

Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels.

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations.

Interactions resulting in a contraindication

The use of carbamazepine is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering carbamazepine MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits (see contraindications).

Agents that may raise carbamazepine plasma levels

Since raised plasma carbamazepine levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Analgesics, anti-inflammatory drugs:	dextropropoxyphene
Androgens:	danazol
Antibiotics:	macrolide antibiotics (e.g. erythromycin, clarithrom in),
Antidepressants:	ciprofloxacine
Antiepileptics:	fluoxetine, fluvoxamine, paroxetine, trazodone vigabatrin
Antifungals:	Azoles (e.g. itraconazole, ketoconazole, fluconazole, voricona le). Alternative anti-convulsants may be recommended in patients t ated with voriconazole or itraconazole
Antihistamines:	loratadine
Antipsychotics:	olanzapine
Antituberculosis:	isoniazid
Antivirals:	protease inhibitors for HIV treatment (e.g. ritonavir)
Carbonic anhydrase inhibitors:	acetazolamide
Cardiovascular drugs:	diltiazem, verapamil
Gastrointestinal drugs:	possibly cimetidine, omeprazole
Other interactions:	Grapefruit juice, nicotinamide (only in high dosage).

Agents that may raise the active metabolite carbamazepine-10, 11-epoxide plasma levels

Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Quetiapine, primidone, progabide, valproic acid, valnoctamide and valpromide.

Agents that may decrease carbamazepine plasma levels

The dose of carbamazepine may have to be adjusted when used concomitantly with the substances described below:

Antiepileptics:	oxcarbazepine, phenobarbital, phenytoin (to avoid phen toin intoxication and subtherapeutic concentrations of carbamazepin it is recommended to adjust the plasma concentration of phenytoin 13 micrograms /mL before adding carbamazepine to the treatment and fosphenytoin, primidone, and, although the data are rtly contradictory, possibly also clonazepam
Antineoplastics:	cisplatin or doxorubicin
Antituberculosis:	rifampicin
Bronchodilatators or anti-asthma drugs:	theophylline, aminophylline
Dermatological drugs:	isotretinoin
Other interactions:	Herbal preparations containing St John's wort (Hype cum perforatum).

Effect of carbamazepine on plasma levels of concomitant agents

Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirement:

Analgesics, anti-inflammatory agents:	buprenorphine, methadone, paracetamol (long term administrati n of carbamazepine and paracetamol (acetaminophen) may be asso ated with hepatotoxicity), tramadol
Antibiotics:	doxycycline, rifabutin
Anticoagulants:	oral anticoagulants (e.g. warfarin, acenocoumarol, rivarox ban,

	dabigatran, apixaban and edoxaban)
Antidepressants:	Bupropion, citalopram, mianserin, sertraline, trazodone, tri clic antidepressants (e.g. imipramine, amitriptyline, nortript ine, clomipramine).
Antiemetics:	aprepitant
Antiepileptics:	clobazam, clonazepam, ethosuximide, lamotrigine, eslicarbaze ine, oxcarbazepine, primidone, tiagabine, topiramate, valproic cid, zonisamide. To avoid phenytoin intoxication and subtherap utic concentrations of carbamazepine it is recommended to adjus the plasma concentration of phenytoin to 13 micrograms/ml b fore adding carbamazepine to the treatment. There have been rare re orts of an increase in plasma mephenytoin levels
Antifungals:	itraconazole, voriconazole. Alternative anti-convulsants ma be recommended in patients treated with voriconazole or itraconazo
Antihelmintics:	albendazole
Antineoplastics:	imatinib, cyclophosphamide, lapatinib, temsirolimus
Antipsychotics:	clozapine, haloperidol and bromperidol, olanzapine, quetia ine, risperidone, aripiprazole, paliperidone
Antivirals:	protease inhibitors for HIV treatment (e.g. indinavir, rito vir, saquinavir)
Anxiolytics:	alprazolam
Bronchodilatators or anti-asthma drugs:	theophylline
Contraceptives:	hormonal contraceptives (alternative contraceptive methods s uld be considered)
Cardiovascular drugs:	calcium channel blockers (dihydropyridine group) e.g. felod ine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabra ne
Corticosteroids:	corticosteroids (e.g. prednisolone, dexamethasone)
Drugs used in erectile dysfunction:	tadalafil
Immunosuppressants:	ciclosporin, everolimus, tacrolimus, sirolimus
Thyroid agents:	levothyroxine
Other drug interactions:	Products containing oestrogens and/or progesterones.

Combinations that require specific consideration

Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity.

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

The combination of lithium and carbamazepine may cause enhanced neurotoxicity in spite of lithium plasma concentrations being within the therapeutic range. Combined use of carbamazepine with metoclopramide or major tranquillisers, e.g. haloperidol, thioridazine, may also result in an increase in neurological side-effects.

Concomitant medication with carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

Carbamazepine may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium). Their dosage should be raised and patients monitored closely for a more rapid recovery from neuromuscular blockade than expected.

Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. It is therefore advisable for the patient to abstain from alcohol.

Concomitant use of carbamazepine with direct acting oral anti-coagulants (rivaroxaban, dabigatran, apixaban and edoxaban) may lead to reduced plasma concentrations of direct acting oral anti-coagulants, which carries the risk of thrombosis. Therefore, if a concomitant use is necessary, closer monitoring of signs and symptoms of thrombosis is recommended.

Interference with serological testing

Carbamazepine may result in false positive perphenazine concentrations in HPLC analysis due to interference.

Carbamazepine and the 10,11-epoxide metabolite may result in false positive tricyclic antidepressant concentration in fluorescence polarized immunoassay method.

4.6 Fertility, pregnancy and lactation

Pregnancy

Offspring of epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. Developmental disorders and malformations, including spina bifida, and also other congenital anomalies e.g. craniofacial defects such as clept lip/palate, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with the use of carbamazepine. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. Based on data in a North American pregnancy registry, the rate of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed within 12 weeks of birth was 3.0% (95% CI 2.1 to 4.2%) among mothers exposed to carbamazepine monotherapy in the first trimester and 1.1% (95% CI 0.35 to 2.5%) among pregnant women not taking any antiepileptic drug (relative risk 2.7, 95% CI 1.1 to 7.0).

Taking these data into consideration:

- pregnant women with epilepsy should be treated with special care

- if women receiving carbamazepine become pregnant or plan to become pregnant, or if the problem of initiating treatment with carbamazepine arises during pregnancy, the drug's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy

- in women of childbearing potential carbamazepine should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic drugs is greater than in those of mothers receiving the individual drugs as monotherapy. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific drugs used and may be higher in polytherapy combinations that include valproate.

- minimum effective doses should be given and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range 4 to 12 micrograms/mL provided seizure control is maintained. There is evidence to suggest that the risk of malformation with carbamazepine may be dose-dependent i.e. at a dose < 400 mg per day, the rates of malformation were lower than with higher doses of carbamazepine.

- patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening

- during pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention

Folic acid deficiency is known to occur in pregnancy. Anti-epileptic drugs have been reported to aggravate deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy.

In the neonate

In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K_1, be given to the mother during the last weeks of pregnancy as well as to the neonate.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal carbamazepine and other concomitant antiepileptic drug use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal carbamazepine use. These reactions may represent a neonatal withdrawal syndrome.

Animal studies have shown reproductive toxicity (see section 5.3).

Breast-feeding

Carbamazepine passes into the breast milk (about 25-60% of the plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking carbamazepine may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction). There have been some reports of cholestatic hepatitis in neonates exposed to carbamazepine during antenatal and or during breast-feeding. Therefore breast-fed infants of mothers treated with carbamazepine should be carefully observed for adverse hepatobiliary effects.

Females and males of reproductive potential

Contraception

Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of child bearing potential should use effective contraception during treatment with carbamazepine and for a period of 28 days after discontinuation of treatment. According to national recommendations (FSRH Clinical Guidance: Drug Interactions with Hormonal Contraception), women taking carbamazepine should preferably change to a contraceptive method unaffected by enzyme inducing drugs (i.e. copper IUDs and the levonorgestrel-releasing IUD or depot progestogen-only injections).

Fertility

There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

4.7 Effects on ability to drive and use machines

The patient's ability to react may be impaired by the medical condition resulting in seizures and adverse reactions including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision reported with carbamazepine, especially at the start of treatment or in connection with dose adjustments. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

Particularly at the start of treatment with carbamazepine, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g.

CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions.

The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and divide the daily dosage into smaller (i.e. 3-4) fractional doses.

Tabulated summary of adverse drug reactions compiled from clinical trials and from spontaneous reports

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10) common (≥1/100, <1/10), uncommon (≥1/1.000, <1/100), rare (≥1/10.000, </1.000), very rare (<1/10.000), not known (cannot be estimated from the available data).

Infections and infestations

Not known**: reactivation of Human herpesvirus 6 infection

Blood and lymphatic system disorders

Very common: leukopenia
Common: thrombocytopenia, eosinophilia
Rare: leucocytosis, lymphadenopathy
Very rare: agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia
Not known: bone marrow depression

Immune system disorders

Rare: a delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, colon)
Very rare: anaphylactic reaction, oedema angioedema, hypogammaglobinaemia
Not known**: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Endocrine disorders

Common: oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders
Very rare: gynaecomastia, galactorrhoea

Metabolism and nutrition disorders

Rare: folate deficiency, decreased appetite
Very rare: porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda)

Psychiatric disorders

Rare: hallucinations (visual or auditory), depression, aggression, agitation, restlessness,

	confusional state
Very rare:	activation of psychosis

Nervous system disorders

Very common:	ataxia, dizziness, somnolence
Common:	diplopia, headache
Uncommon:	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus
Rare:	dyskinesia, eye movement disorder, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, and paresis
Very rare:	neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia
Not known**:	sedation, memory impairment

Eye disorders

Common:	accommodation disorders (e.g. blurred vision)
Very rare:	lenticular opacities, conjunctivitis

Ear and labyrinth disorders

Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception

Cardiac disorders

Rare:	cardiac conduction disorders
Very rare:	arrhythmia, atrioventricular block with syncope, bradycardia, cardiac failure congestive, coronary artery disease aggravated

Vascular disorders

Rare:	hypertension or hypotension
Very rare:	circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis

Respiratory, thoracic and mediastinal disorders

Very rare:	pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia

Gastro-intestinal disorders

Very common:	nausea, vomiting
Common:	dry mouth, with suppositories rectal irritation may occur
Uncommon:	diarrhoea, constipation
Rare:	abdominal pain
Very rare:	pancreatitis, glossitis, stomatitis
Not known**:	colitis

Hepatobiliary disorders

Rare:	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice
Very rare:	hepatic failure, granulomatous liver disease

Skin and subcutaneous tissue disorders

Very common:	urticaria, which may be severe dermatitus allergic
Uncommon:	dermatitis exfoliative
Rare:	systemic lupus erythematosus, pruritus
Very rare:	Stevens-Johnson syndrome*, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism.

Not known**: acute generalized exanthematous pustulosis (AGEP)**, lichenoid keratosis, onychomadesis

Musculoskeletal, connective tissue and bone disorders

Rare: muscular weakness

Very rare: bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms

Not known**: fracture

Renal and urinary disorders

Very rare: tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria and blood urea/azotaemia), urinary retention, urinary frequency

Reproductive system

Very rare: sexual disturbances/erecticle dysfunction spermatogenesis abnormal (with decreased sperm count and/or motility)

General disorders and administration site conditions

Very common: fatigue

Investigations

Very common: gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant

Common: blood alkaline phosphatase increased

Uncommon: transaminases increased

Very rare: intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased

Not known**: bone density decreased.

Injury, poisoning and procedural complications

Not known**: fall (associated with carbamazepine treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4 Special warnings and precautions).

*In some Asian countries also reported as rare. See also section 4.4 Special warnings and precautions for use.

**Additional adverse drug reactions from spontaneous reports (frequency not known)

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with carbamazepine. The mechanism by which carbamazepine affects bone metabolism has not been identified.

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous ADRs such as SJS, TEN, DRESS, AGEP and maculopapular rash. In Japanese and European patients, these reactions have been reported to be associated with the use of carbamazepine and the presence of the HLA-A*3101 allele. Another marker, HLA-B*1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry (see sections 4.2 and 4.4 for further information).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, respiratory systems and the adverse drug reactions mentioned under section 4.8.

Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

Respiratory system: Respiratory depression, pulmonary oedema.

Cardiovascular system: Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.

Gastro-intestinal system: Vomiting, delayed gastric emptying, reduced bowel motility.

Musculoskeletal system: There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.

Renal function: Retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of carbamazepine.

Laboratory findings: Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatine phosphokinase.

Treatment

There is no specific antidote.

Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose.

Evacuation of the stomach, gastric lavage, and administration of activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations

Charcoal haemoperfusion has been recommended. Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose.

Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptic, neurotropic and psychotropic agent; ATC Code: N03A FO1. Dibenzazepine derivative.

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonic-clonic seizures, as well as combinations of these types of seizures.

The mechanism of action of carbamazepine, the active substance of carbamazepine, has only been partially elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be responsible for the antimanic properties of carbamazepine.

5.2 Pharmacokinetic properties

Absorption

Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours (chewable tablets 6 hours; syrup 2 hours) following single oral doses. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400 mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx. 4.5µg/ml.

The bioavailability of carbamazepine in various oral formulations has been shown to lie between 85-100%.

Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of carbamazepine.

Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Different preparations of carbamazepine may vary in bioavailability; to avoid reduced effect or risk of breakthrough seizures or excessive side effects, it may be prudent to avoid changing the formulation.

Distribution

Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels.

Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 l/kg.

Biotransformation

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites.

Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11-epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related

to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.

Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Elimination

The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found.

The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.

After administration of a single oral dose of 400 mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10, 11-epoxide metabolite.

Characteristics in patients

The steady-state plasma concentrations of carbamazepine considered as “therapeutic range” vary considerably inter-individually; for the majority of patients a range between 4-12 µg/ml corresponding to 17-50 µmol/l has been reported. Concentrations of carbamazepine 10, 11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.

Special populations

Paediatric populations

Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults to maintain therapeutic concentrations.

Elderly population (65 years or above)

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.

Patients with hepatic or renal impairment

No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, local tolerance, genotoxicity and carcinogenic potential. Reproductive toxicity studies in animals were insufficient to rule out a teratogenic effect of carbamazepine in humans.

Carcinogenicity

In rats treated with carbamazepine for two years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no evidence to date that these observations are of any relevance to the therapeutic use of carbamazepine in humans.

Reproductive toxicity

Animal data

Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

The cumulative evidence from various animal studies in mice, rats and rabbits indicates that carbamazepine has no or only minor teratogenic potential at doses relevant to man. However, the animal studies were insufficient to rule out a teratogenic effect of carbamazepine. In a reproduction study in rats, nursing offspring demonstrated a reduced weight gain at a maternal dosage level of 192 mg/kg/day.

Fertility

In chronic toxicity studies dose related testicular atrophy and aspermatogenesis occurred in rats receiving carbamazepine. The safety margin for this effect is not known.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Sodium Saccharin	BP
Propylene Glycol	BP
Glycerine	BP
Sorbitol 70 %	BP
Colour Tartrazine Supra	INH
Essence Pineapple No.1	INH
Propyl Paraben Plain	BP

6.2 Incompatibilities:
None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Store under normal storage conditions (15ºC-30ºC) Protect from light.

6.5 Nature and Contents of Container:
250 ml solution in one bottle. Such bottle packed in carton with pack insert. Such carton packed and export in worthy shipper.

6.6 Special precautions for disposal:
None reported.

7. Registrant:
AGOG PHARMA LTD.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane,
India.

8. Manufacturer:

Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

AGOG PHARMA LTD.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane,
India.

9. Date of revision of the text: