AGOG Pharma Ltd.
(WHO - GMP CERTIFIED - GOVT RECOGNISED EXPORT HOUSE)
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1.5 PRODUCT INFORMATION

1.5.1 Prescribing Information (Summary of Products Characteristics)

1. NAME OF DRUG PRODUCT

1. Name of drug product

HALOPERIDOL BP 5 MG TABLETS

1.1 (Trade) name of product

AGOHAL-5 TABLETS

1.2 Strength

Each uncoated tablet contains:
Haloperidol BP 5 mg

1.3 Pharmaceutical Dosage Form

Uncoated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

2.1 Qualitative Declaration

Each uncoated tablet contains:
Haloperidol BP 5 mg

2.2 Quantitative Declaration

Ingredients	Specification	Label Claim	Qty. / Tab.
ACTIVE			
Haloperidol	BP	5 mg	5.000 mg
INACTIVE			
Lactose	BP	-	59.85 mg
Maize starch (10% extra added to compensate LOD.)	BP	-	31.25 mg
Poly vinyl pyrrolidone	BP	-	1.875 mg
Isopropyl Alcohol	BP	-	30.00 mg
Talcum	BP	-	3.000 mg
Magnesium stearate	BP	-	1.000 mg
Colloidal silicon dioxide	BP	-	2.000 mg
Sodium starch glycolate	BP	-	4.000 mg
Cross Carmellose Sodium	BP	-	5.000 mg

BP = British Pharmacopoeia.

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3. PHARMACEUTICAL DOSAGE FORM

Uncoated tablets

White, circular, flat, uncoated tablets having break line on one side and other side is plain of each tablet.

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4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Haloperidol is a high potency first-generation (typical) antipsychotic and one of the most frequently used antipsychotic medications used worldwide. While haloperidol has demonstrated pharmacologic activity at a number of receptors in the brain, it exerts its antipsychotic effect through its strong antagonism of the dopamine receptor (mainly D2), particularly within the mesolimbic and mesocortical systems of the brain. Haloperidol is indicated for the treatment of the manifestations of several psychotic disorders including schizophrenia, acute psychosis, Tourette syndrome, and other severe behavioural states. It is also used off-label for the management of chorea associated with Huntington's disease and for the treatment of intractable hiccups as it is a potent antiemetic. Dopamine-antagonizing medications such as haloperidol are though to improve psychotic symptoms and states that are caused by an over-production of dopamine, such as schizophrenia, which is theorized to be caused by a hyperdopaminergic state within the limbic system of the brain.

4.2 Posology and Method of Administration

Haloperidol in psychosis: In this instance, the oral forms can be used. For moderate symptomology: 0.5 to 2 mg 2 to 3 times a day orally. In some resistant cases, up to 30 mg/day may be necessary.

Haloperidol in schizophrenia: In moderately severe patients, dosing is 0.5 to 2 mg haloperidol orally 2 to 3 times a day. It should not exceed 30 mg daily in case of severe cases. To control acute agitation in a schizophrenic patient, dosing is 2 to 5 mg haloperidol intramuscularly every 4 to 8 hours.

Haloperidol in Tourette syndrome: Dosing is 0.5 to 2 mg orally 2 to 3 times a day in the moderately symptomatic cases, and for severe cases, it can be higher: 3 to 5 mg, 2 to 3 times a day.

Pediatric Use: Safety, effectiveness, and doses of haloperidol in the pediatric population have not been established yet.

Geriatric Use: the prevalence of tardive dyskinesia is the highest among older patients, especially older women.

Adult Dosage:

Individualize. Initially: Moderate symptoms: 0.5mg–2mg 2–3 times daily. Severe, chronic, or resistant symptoms: 3mg–5mg 2–3 times daily. Debilitated: 0.5mg–2mg 2–3 times daily. Max: 100mg/day.

Children Dosage:

<3yrs: not recommended. Total dose may be divided, to be given 2–3 times daily. ≥3yrs: initially 0.5mg daily, may increase at increments of 0.5mg at 5–7 day intervals.

Psychosis: 0.05mg/kg/day–0.15mg/kg/day. Nonpsychotic behavior and Tourette's: 0.05mg/kg/day–0.075mg/kg/day. Max 6mg/day.

4.3 Contraindications

Haloperidol is contraindicated if there is documented hypersensitivity to this drug, in Parkinson disease, dementia with Lewy body, comatose patient, in any condition with the depressed central nervous system (CNS). Since many drugs (barbiturates, benzodiazepines, and opioids) can cause depression to CNS, concurrent use of haloperidol should be avoided or used with great caution.

4.4 Special Warnings and Precautions for Use

Haloperidol prolongs the hypnotic action of barbiturates and may potentiate the effects of alcohol and other central nervous system depressant drugs, such as anesthetics and narcotics; caution should therefore be exercised when it is used with agents of this type and adjustments in its dosage may be required.

Haloperidol may lower the convulsive threshold and has been reported to trigger seizures in previously controlled known epileptics. When instituting haloperidol therapy in these patients, adequate anticonvulsant medication should be maintained concomitantly.

Elderly or debilitated patients receiving the drug should be carefully observed for any evidence of over sedation which might lead to dehydration and reduced pulmonary ventilation and could result in complications, such as terminal bronchopneumonia.

Although haloperidol is a relatively non-sedating neuroleptic, sedation may occur in some patients.

Therefore, physicians should be aware of this possibility and caution patients about the danger of participating in activities requiring complete mental alertness, judgment and physical coordination, such as driving and operating dangerous machinery.

Haloperidol has been reported to interfere with the anticoagulant properties of phenindione in an isolated case and the possibility should be kept in mind of a similar effect occurring when haloperidol is used with other anticoagulants.

Administration to patients with severe cardiac involvement should be guarded, despite the fact that haloperidol is well tolerated by patients with cardiac insufficiency and that it has been used with favorable results to maintain the cardiovascular function of patients with excitive crises. In very rare instances, it has been felt that haloperidol was contributory to the precipitation of attacks in angina-prone patients. Moderate hypotension may occur with parenteral administration or excessive oral doses of haloperidol; however, vertigo and syncope occur only rarely.

Haloperidol has lowered the level of cholesterol in the serum and liver of monkeys. An accumulation of desmosterol has been observed in the serum of rats given repeated high doses (10 mg/kg) of haloperidol. In man, mild transient decreases in serum cholesterol were reported in preliminary studies. However, in a study involving a group of schizophrenic patients on extended medication, significant lowering of serum cholesterol was not observed with haloperidol and there was no accumulation of desmosterol or 7-dehydrocholesterol. A significant lowering of cholesterol together with an accumulation of another sterol (possibly 7-dehydrocholesterol) has been reported in patients receiving a chemically related drug (trifluperidol) and skin and eye changes (ichthyosis and cataracts) have occurred clinically with another butyrophenone derivative. Skin and eye changes have not been observed in patients receiving haloperidol. However, it is advisable that all patients receiving haloperidol for a prolonged period of time be carefully observed for any changes in the skin and eyes. If such changes are seen, the drug should be discontinued promptly.

Tardive dyskinesias are known to occur in patients on long-term antipsychotic therapy, including haloperidol. This should be borne in mind when using neuroleptics, and if possible, the dosage should be reduced or the drug discontinued when manifestations of this syndrome are detected. The antiemetic action of haloperidol may obscure signs of toxicity due to over dosage of other drugs or mask the symptoms of some organic diseases, such as brain tumor or intestinal obstruction.

If an antiparkinson agent is used concomitantly with haloperidol, both drugs should not be discontinued simultaneously, since extrapyramidal symptoms may occur due to the slower excretion rate of haloperidol.
Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs.

Neither clinical studies nor epidemiologic studies conducted to date, however have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered to be too limited to be conclusive at this time.

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use.

Endocrine and Metabolism:
Hyperglycemia: Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Hyperprolactinemia: Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Genitourinary: Rare cases of priapism have been reported with antipsychotic use, such as haloperidol. This adverse reaction, as with other psychotropic drugs, did not appear to be dose dependent and did not correlate with the duration of treatment.

4.5 Interaction with Other Drugs, Other Forms of Interactions

Neurological: Neuromuscular (extrapyramidal) effects such as Parkinson-like symptoms, akathisia, dyskinesia, dystonia, hyper-reflexia, rigidity, opisthotonas, and occasionally, oculogyric crisis are the most frequently reported side effects associated with the administration of haloperidol.
Headache, vertigo and cerebral seizures have also been reported. The extra pyramidal reactions are usually dose-related in occurrence and severity and as a rule, tend to subside when the dose is reduced or the drug is temporarily discontinued. However, considerable inter-patient variability exists and although some individuals may tolerate higher than average

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doses of haloperidol, severe extra pyramidal reactions necessitating discontinuation of the drug, may occur at relatively
low doses. Administration of an anti-Parkinson agent is usually but not always effective in preventing or reversing neuromuscular reactions associated with haloperidol.

Tardive Dyskinesias: As with all antipsychotic agents, tardive dyskinesia may appear on some patients on long-term therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes they may be accompanied by involuntary movements of extremities.

There is no known effective treatment for tardive dyskinesia; anti-Parkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment or increase the dosage of the agent or switch to a different antipsychotic agent, the syndrome may be masked.
The physician may be able to reduce the risk of this syndrome by minimizing the unnecessary use of neuroleptic drugs and reducing the dose or discontinuing the drug if possible, when manifestations of this syndrome are recognized particularly in patients over the age of 50. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Behavioural: Insomnia, depressive reactions and toxic confusional states are the more common effects encountered. Drowsiness, lethargy, stupor and catalepsy, confusion, restlessness, agitation, anxiety, euphoria and exacerbation of psychotic symptoms, including hallucinations have also been reported.

Cardiovascular: Tachycardia and hypotension have occurred but severe orthostatic hypotension has not been reported. However, should it occur, supportive measures, including intravenous vasopressors such as norepinephrine may be required.

Autonomic: Dry mouth, blurred vision, urinary retention and incontinence have been reported.

Allergic and Toxic: The overall incidence of significant hematologic changes in patients on haloperidol has been low. Occasionally, there have been reports of mild and usually transient leukopenia and leukocytosis, decreases in blood cell counts, anemia and a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported with the use of haloperidol and then only in associated with other medication. Impairment of liver function (jaundice or hepatitis) has been reported rarely. One case of photosensitization is known and isolated cases of idiosyncratic
cutaneous involvement have been observed.

Endocrine: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido and changes in blood sugar levels have been reported.

Gastrointestinal: Heartburn, nausea, vomiting, anorexia, weight loss, constipation, diarrhea and hypersalivation have been reported.

Miscellaneous: Other untoward effects encountered include peripheral edema,

hypocholesterolemia, hyperpyrexia, alopecia, laryngospasm, bronchospasm and increased depth of respiration, stasis pneumonia and a syndrome characterized by perspiration, dehydration, hyperthermia and a dazed state of mine (if this occurs the drug should be discontinued).

4.6 Use in Pregnancy and Lactation

There are no well-controlled studies for the haloperidol use in pregnant women. But there are several reports, however, of cases of limb malformations in the newborn whose mother used haloperidol, but causal relationships were not appropriately established in these cases. Since these experiences do not exclude the possibility of a fetal anomaly due to haloperidol, this drug should be used only if the benefit outweighs the potential risk to the fetus.

4.7 Undesirable effects

Due to the blockade of the dopamine pathway in the brain, typical antipsychotic medications such as haloperidol have correlations with extrapyramidal side effects.

Extrapyramidal symptoms

- Acute Dystonia - (Develops within hours to days of initiation. Maybe presented as muscle spasm, stiffness, oculogyric crisis)
- Akathisia - (Develops within days to months of use of haloperidol - characterized by restlessness.)
- Neuroleptic malignant syndrome - (NMS; infrequent but severe condition. May present as High fever, muscle rigidity)
- Parkinsonism - (Develops after days to month use of haloperidol)
- Tardive dyskinesia - (Develops after years. Presents as chore especially orofacial region)

Common

- Anticholinergic effects - (Elevated temperature, dry mouth, drowsiness or sedation, constipation, urinary retention)
- Sedation
- Weight gain
- Erectile dysfunction in male
- Oligomenorrhea or amenorrhea in female

Less common

- Orthostatic hypotension - (After IM injection of haloperidol), tachycardia, palpitation
- Agitation, generalized anxiety, cerebral edema, new-onset depression, dizziness, euphoric mood, headache, sleeplessness, poikilothermia, restlessness, generalized weakness, confusion
- Anorexia, constipation, dyspepsia, ileus, decreased gag reflex.
- Lens opacities - (If used for a prolonged time)

Uncommon

- ECG changes - (QT prolongation, torsades de pointes)
- Photosensitivity reaction
- Generalized pruritus
- Diarrhea, gastrointestinal distress
- Blood dyscrasia
- Ejaculatory problems

Rare

- Seizure
- Cholestatic jaundice
- Priapism

4.8 Overdoses

Toxicities are the exaggerated symptoms of known pharmacologic effects and known adverse reactions. The most prominent toxicities of haloperidol are 1) severe extrapyramidal symptoms, hypotension, sedation. The patient may appear comatose with severe respiratory depression or shock from hypotension. The extrapyramidal symptoms are muscular weakness or rigidity, a generalized or localized tremor that may be characterized by the akinetic or agitations types of movements, respectively. Haloperidol overdose is also associated with ECG changes known as torsade de pointes, which may cause arrhythmia or cardiac arrest.

Since there is no specific antidote, supportive treatment is the mainstay of haloperidol toxicity. If a patient develops sign symptoms of toxicities, the clinician should consider gastric lavage or induction of emesis as soon as possible, followed by the administration of activated charcoal. Maintenance of Airway, Breathing, and circulation are the most important factors for survival. A patent airway must be ensured by the use of an oropharyngeal airway or endotracheal tube or by tracheostomy if the patient is in a coma. Respiratory depression can be managed by artificial respiration or by mechanical respirators in severe cases or a comma.

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Hypotension and circulatory collapse are manageable by using intravenous fluids, concentrated albumin, and vasopressor agents (phenylephrine or norepinephrine).

Epinephrine should not be used as it can decrease blood pressure. If the patient develops severe extrapyramidal reactions, antiparkinson medication should be considered. ECG and vital signs require monitored at regular intervals. Especially for signs of torsades de Pointes or Q-T prolongation or dysrhythmias, cardiac monitoring should be in place until the ECG becomes normal. If the patient develops arrhythmias, which could be life-threatening, prompt management should commence with appropriate anti-arrhythmic measures.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmaco-Kinetic Properties

Absorption

Haloperidol is a highly lipophilic compound and is extensively metabolized in humans, which may cause a large interindividual variability in its pharmacokinetics. Studies have found a wide variance in pharmacokinetic values for orally administered haloperidol with 1.7-6.1 hours reported for time to peak plasma concentration (tmax), 14.5-36.7 hours reported for half-life ($t_{1/2}$), and 43.73 μg/L•h [range 14.89 -120.96 μg/L•h] reported for AUC. Haloperidol is well-absorbed from the gastrointestinal tract when ingested orally however the first-pass hepatic metabolism decreases its oral bioavailability to 40 - 75%.

After intramuscular administration, the time to peak plasma concentration (tmax) is 20 minutes in healthy individuals or 33.8 minutes in patients with schizophrenia, with a mean half-life of 20.7 hours. Bioavailability following intramuscular administration is higher than that for oral administration.

Administration of haloperidol decanoate (the depot form of haloperidol for long-term treatment) in sesame oil results in slow release of the drug for long-term effects. The plasma concentrations of haloperidol gradually rise, reaching its peak concentration at about 6 days after the injection, with an apparent half-life of about 21 days. Steady-state plasma concentrations are achieved after the third or fourth dose.

Volume of distribution

The apparent volume of distribution was found to range from 9.5-21.7 L/kg. This high volume of distribution is in accordance with its lipophilicity, which also suggests free movement through various tissues including the blood-brain barrier.

Protein binding

Studies have found that free fraction of haloperidol in human plasma is 7.5-11.6%. This was found to be comparable among healthy adults, young adults, elderly patients with schizophrenia, and even in patients with liver cirrhosis.

Metabolism

Haloperidol is extensively metabolised in the liver with only about 1% of the administered dose excreted unchanged in urine.
In humans, haloperidol is biotransformed to various metabolites, including p-fluorobenzoylpropionic acid, 4-(4-chlorophenyl)-4-hydroxypiperidine, reduced

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haloperidol, pyridinium metabolites, and haloperidol glucuronide. In psychiatric patients treated regularly with haloperidol, the concentration of haloperidol glucuronide in plasma is the highest among the metabolites, followed, in rank order, by unchanged haloperidol, reduced haloperidol and reduced haloperidol glucuronide.

The drug is thought to be metabolized primarily by oxidative N-dealkylation of the piperidine nitrogen to form fluorophenylcarbonic acids and piperidine metabolites (which appear to be inactive), and by reduction of the butyrophenone carbonyl to the carbinol, forming *hydroxyhaloperidol*.

The enzymes involved in the biotransformation of haloperidol include cytochrome P450 (CYP) including CYP3A4 and CYP2D6, carbonyl reductase and uridine di-phosphoglucoseglucuronosyltransferase enzymes. The greatest proportion of the intrinsic hepatic clearance of haloperidol is performed by glucuronidation and followed by the reduction of haloperidol to reduced haloperidol and by CYP-mediated oxidation.

In studies of cytochrome-mediated disposition in vitro, CYP3A4 appears to be the major isoform of the enzyme responsible for the metabolism of haloperidol in humans. The intrinsic clearance of the back-oxidation of reduced haloperidol to the parent compound, oxidative N-dealkylation and pyridinium formation are of the same order of magnitude. This suggests that the same enzyme system is responsible for the above three metabolic reactions.

In vivo human studies on haloperidol metabolism have shown that the glucuronidation of haloperidol accounts for 50 to 60% of haloperidol biotransformation and that approximately 23% of the biotransformation was accounted for by the reduction pathway. The remaining 20 to 30% ofthe biotransformation of haloperidol would be via N-dealkylation and pyridinium formation

Hover over products below to view reaction partners

- Haloperidol
  - 4-(4-chlorophenyl)-4-hydroxypiperidine
  - Reduced haloperidol
    - Haloperidol reduced pyridinium ion derivative
      - Haloperidol pyridinium ion derivative
  - Haloperidol glucuronide
  - Haloperidol 1,2,3,6-tetrahydropyridine
    - Haloperidol pyridinium ion derivative
  - fluorobenzoylpropionic acid

- 4-(4-Chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-pyridinium (HPP+)
- p-Fluorobenzoylpropionic acid and 4-(4-chlorophenyl)-4-hydroxypiperidine

Route of elimination

In radiolabeling studies, approximately 30% of the radioactivity is excreted in the urine following a single oral administration of 14C-labelled haloperidol, while 18% is excreted in the urine as haloperidol glucuronide, demonstrating that haloperidol glucuronide is a major metabolite in the urine as well as in plasma in humans.

5.2 Pharmaco-dynamic properties

Use of the first-generation antipsychotics (including haloperidol) is considered highly effective for the management of the "positive" symptoms of schizophrenia including hallucinations, hearing voices, aggression/hostility, disorganized speech, and psychomotor agitation. However, this class is limited by the development of movement disorders such as drug-induced parkinsonism, akathisia, dystonia, and tardive dyskinesia, and other side effects including sedation, weight gain, and prolactin changes. Compared to the lower-potency first-generation antipsychotics such as Chlorpromazine, Zuclopenthixol, Fluphenazine, and Methotrimeprazine, haloperidol typically demonstrates the least amount of side effects within class, but demonstrates a stronger disposition for causing extrapyramidal symptoms (EPS).[6,7,8] Low-potency medications have a lower affinity for dopamine receptors so that a higher dose is required to effectively treat symptoms of schizophrenia. In addition, they block many receptors other than the primary target (dopamine receptors), such as cholinergic or histaminergic receptors, resulting in a higher incidence of side effects such as sedation, weight gain, and hypotension

The balance between the wanted drug effects on psychotic symptoms and unwanted side effects are largely at play within dopaminergic brain pathways affected by haloperidol. Cortical dopamine-D2-pathways play an important role in regulating these effects and include the nigrostriatal pathway, which is responsible for causing extrapyramidal symptoms (EPS), the mesolimbic and mesocortical pathways, which are responsible for the improvement in positive schizophrenic symptoms, and the tuberoinfundibular dopamine pathway, which is responsible for hyperprolactinemia.

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome.

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Cases of sudden death, QT-prolongation, and Torsades de Pointes have been reported in patients receiving haloperidol. Higher than recommended doses of any formulation and intravenous administration of haloperidol appear to be associated with a higher risk of QT-prolongation and Torsades de Pointes. Although cases have been reported even in the absence of predisposing factors, particular caution is advised in treating patients with other QT-prolonging conditions (including electrolyte imbalance [particularly hypokalemia and hypomagnesemia], drugs known to prolong QT, underlying cardiac abnormalities, hypothyroidism, and familial long QT-syndrome).

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose	BP	59.85	mg
Maize starch (10% extra added to compensate LOD.)	BP	31.25	mg
Poly vinyl pyrrolidone	BP	1.875	mg
Isopropyl Alcohol	BP	30.00	mg
Talcum	BP	3.000	mg
Magnesium stearate	BP	1.000	mg
Colloidal silicon dioxide	BP	2.000	mg
Sodium starch glycolate	BP	4.000	mg
Cross Carmellose Sodium	BP	5.000	mg

6.2 Incompatibilities

None reported

6.3 Shelf-Life

36 months from the date of manufacture.

6.4 Special Precautions for Storage

Store below 30°C.
Protect from light.

6.5 Nature and Contents of Container

Jar pack of 1000 tablets