EXCELXIN 40/320 TABLET

Summary Product Characteristics (SPC)

1 NAME OF THE MEDICINAL PRODUCT

EXCELXIN 40/320 TABLET, Dihydroartemisinin 40 mg and Piperaquine 320 mg, Film coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Dihydroartemisinin 40 mg
Piperaquine Phosphate 320 mg
Excipients Q.S.
For a full list of excipients, refer section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the treatment of uncomplicated Plasmodium falciparum malaria in adults, adolescents, children and infants 6 months and over and weighing 5 kg or more.

4.2 Posology and method of administration

Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should be administered over three consecutive days for a total of three doses taken at the same time each day.

Posology

Tablet should be administered over three consecutive days for a total of three doses taken at the same time each day. If a patient vomits within 30 minutes, the whole dose should be re-administered; if a patient vomits within 30-60 minutes, half the dose should be re-administered. Re-dosing should not be attempted more than once. If the second dose is vomited, alternative antimalarial therapy should be instituted. If a dose is missed, it should be taken as soon as realised and then the recommended regimen continued until the full course of treatment has been completed. There is no data on a second course of treatment.
No more than two courses may be given within a 12 month period.
A second course should not be given within 2 months after the first course due to the long elimination half-life of piperaquine.

Special populations
Elderly
Clinical studies did not include patients aged 65 years and over, therefore no dosing recommendation can be made. Considering the possibility of age-associated decrease in hepatic and renal function, as well as a potential for heart disorders, caution should be exercised when administering the product to the elderly.
Hepatic and renal impairment. It has not been evaluated in subjects with moderate or

severe renal or hepatic insufficiency.
Paediatric population
The safety and efficacy in infants aged less than 6 months and in children weighing less than 5 kg has not been established. No data are available for these paediatric subsets.

Method of administration
Should be taken orally with water and without food. Each dose should be taken no less than 3 hours after the last food intake. No food should be taken within 3 hours after each dose. For patients unable to swallow the tablets, such as infants and young children, tablet may be crushed and mixed with water. The mixture should be used immediately after preparation.

4.2 Contraindications

-Family history of sudden death or of congenital prolongation of the QTc interval.
-Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval.
-History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
-Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
-Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
-Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):
• Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
• Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive medicinal products.
• Certain antimicrobial medicinal products, including medicinal products of the following classes:
- macrolides (e.g. erythromycin, clarithromycin),
- fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
- imidazole and triazole antifungalmedicinal products,
- and also pentamidine and saquinavir.
• Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine). Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.

4.3 Special warnings and precautions for use

Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should not be used to treat severe falciparum malaria and, due to insufficient data, should not be used to treat malaria due to Plasmodium vivax, Plasmodium malariae or Plasmodium ovale.
The long half-life of piperaquine (about 22 days) should be kept in mind in the event that another anti-malarial agent is started due to treatment failure or a new malaria infection.

Piperaquine is a mild inhibitor of CYP3A4. Caution is recommended when co-administering Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets with medicinal products exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic and/or toxic effects of some co-administered medicinal products could be altered.

Piperaquine is also a substrate of CYP3A4. A moderate increase of piperaquine plasma concentrations (<2-fold) was observed when co-administered with strong CYP3A4 inhibitors, resulting in a potential exacerbation of the effect on QTc prolongation.

Exposure to piperaquine may also be increased when co-administered with mild or moderate CYP3A4-inhibitors (e.g. oral contraceptives). Therefore, caution should be applied when co-administering Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets with any CYP3A4-inhibitor and ECG monitoring should be considered.

Due to the lack of multiple dose PK data for piperaquine, administration of any strong CYP3A4-inhibitors should be discouraged after initiation (i.e. the first dose) Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets.

Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should not be used during pregnancy in situations where other suitable and effective antimalarials are available .

In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than two courses of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should be given in a 12-month period.

Effects on cardiac repolarization

In clinical trials with Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets therapy than with the comparators. Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets treated patients than in those treated with comparator antimalarial. Before the third dose of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets, in one of the two Phase III studies 3/767 patients (0.4%) were reported to have a QTcF value of >500 ms versus none in the comparator group.

The potential for Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets to prolong the QTc interval was investigated in parallel groups of healthy volunteers who took each dose with high (~1000 Kcal) or low (~400 Kcal) fat/calorie meals or in fasting conditions. Compared to placebo, the maximum mean increases in QTcF on Day 3 of dosing with Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets were 45.2, 35.5 and 21.0 msec under respective dosing conditions. The QTcF prolongation observed under fasting conditions lasted between 4 and 11 hours after the last dose was administered on Day 3. The mean QTcF prolongation compared to placebo decreased to 11.8 msec at 24 hours and to 7.5 msec at 48 hours. No healthy subject dosed in fasting conditions showed a QTcF greater than 480 msec or an increase over baseline greater than 60 msec. The number of subjects with QTcF greater than 480 msec after dosing with low fat meals was 3/64, while 10/64 had QTcF values over this threshold after dosing with high fat meals. No subject had a QTcF value greater than 500 msec in any

of the dosing conditions.
An ECG should be obtained as early as possible during treatment with Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets and ECG monitoring should be applied in patients who may have a higher risk of developing arrhythmia in association with QTc prolongation.
When clinically appropriate, consideration should be given to obtaining an ECG from all patients before the last of the three daily doses is taken and approximately 4-6 hours after the last dose, since the risk of QTc interval prolongation may be greatest during this period. QTc intervals of more than 500 ms are associated with a pronounced risk for potentially life-threatening ventricular tachyarrhythmias. Therefore, ECG monitoring during the following 24-48 hours should be applied for patients found to have a prolongation to this extent. These patients should not receive another dose of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets and alternative antimalarial therapy should be instituted.
Compared to adult males, female patients and elderly patients have longer QTc intervals. Therefore, they may be more sensitive to the effects of QTc-prolonging medications such as Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets so that special caution is required.

Paediatric population
Special precaution is advised in young children when vomiting, as they are likely to develop electrolyte disturbances. These may increase the QTc-prolonging effect of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets

Hepatic and renal impairment
Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets has not been evaluated in patients with moderate or severe renal or hepatic insufficiency. Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

4.4 Interaction with other medicinal products and other forms of interaction

Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets is contraindicated in patients already taking other medicinal products that are known to prolong the QTc interval due to the risk of a pharmacodynamic interaction leading to an additive effect on the QTc interval.
A limited number of drug-drug pharmacokinetic interaction studies with Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets have been performed in healthy adult subjects. Therefore the assessment of the potential for drug-drug interactions to occur is based on either in vivo or in vitro studies.

Effects co-administered medicinal products
Piperaquine is metabolised by, and is an inhibitor of CYP3A4. The concurrent administration of oral Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets with

7.5 mg oral midazolam, a CYP3A4 probe substrate, led to a modest increase (≤2-fold) in midazolam and its metabolites exposures in healthy adult subjects. This inhibitory effect was no longer evident one week after last administration of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets Therefore, particular attention should be paid when medicinal products that have a narrow therapeutic index (e.g. antiretroviral medicinal products and cyclosporine) are co-administered with Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets From in vitro data, piperaquine undergoes a low level of metabolism by CYP2C19, and is also an inhibitor of this enzyme. There is the potential for reducing the rate of metabolism of other substrates of this enzyme, such as omeprazole, with consequent increase of their plasma concentration, and therefore, of their toxicity.
Piperaquine has the potential to increase the rate of metabolism for CYP2E1 substrates resulting in a decrease in the plasma concentrations of substrates such as paracetamol or theophylline, and the anaesthetic gases enflurane, halothane and isoflurane. The main consequence of this interaction could be a reduction of efficacy of the co-administered medicinal products.

Paediatric population
Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings should be taken into account for the paediatric population.

Oral contraceptives
When co-administered to healthy women, Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets exerted only a minimum effect on an estrogen/progestinic combination oral contraceptive treatment increasing the ethynilestradiol rate of absorption (expressed by geometric mean Cmax) of about 28% but not significantly changing the exposure to ethynilestradiol and levonorgestrel and not influencing contraception activity as demonstrated by the similar plasma concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone observed after oral contraceptive treatment with or without concomitant Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets administration.

Food interaction
Absorption of piperaquine is increased in the presence of fatty food which may increase its effect on QTc interval. Therefore, Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should be taken with water only. Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.5 Pregnancy and lactation

Pregnancy

There are insufficient data on the use of tablets. Based on animal data, Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation . Piperaquine was not teratogenic in the rat or rabbit. In perinatal and postnatal studies in rats, piperaquine was associated with delivery complications. However, there was no delay in neonatal development following exposure in utero or via milk.

Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should not be used during pregnancy in situations where other suitable and effective anti-malarials are available.

Lactation

Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should not breast-feed during their treatment.

4.6 Effects on ability to drive and use machines

Adverse event data collected in clinical trials suggest that Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets has no influence on the ability to drive and operate machines once the patient has recovered from the acute infection.

4.7 Undesirable effects

Summary of the safety profile

The safety of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets has been evaluated in two phase III open-label studies involving 1,239 paediatric patients up to 18 years and 566 adult patients >18 years treated with Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets.

In a randomized trial in which 767 adults and children with uncomplicated P. falciparum malaria were exposed to Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets, 25% of subjects were judged to have experienced an adverse drug reaction (ADR). No single type of ADR occurred at an incidence of ≥5%. The most frequent ADRs observed at an incidence ≥1.0% were: Headache (3.9%), Electrocardiogram QTc Prolonged (3.4%), P. falciparum infection (3.0%), Anaemia (2.8%), Eosinophilia (1.7%), Haemoglobin
decreased (1.7%), Sinus tachycardia (1.7%), Asthenia (1.6%), Haematocrit [decreased]
(1.6%), Pyrexia (1.5%), Red Blood Cell Count decreased (1.4%). A total of 6 (0.8%) subjects had serious ADRs in the study.In a second randomized trial, 1,038 children, aged between 6 months and 5 years, were exposed to Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets and 71% were judged to have experienced an ADR. The following ADRs were observed at an incidence of ≥5.0%: Cough (32%), Pyrexia (22.4%), Influenza (16.0%), P. falciparum infection (14.1%), Diarrhoea (9.4%), Vomiting (5.5%) and Anorexia (5.2%). A total of 15 (1.5%) subjects had serious ADRs

in the study.

The ADRs noted for Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets were generally mild in severity, and the majority were non-serious. Reactions such as cough, pyrexia, headache, P. falciparum infection, anaemia, asthenia, anorexia and the observed changes in blood cell parameters are consistent with those expected in patients with acute malaria. The effect on prolongation of the QTc interval was observed on Day 2, and had resolved by Day 7 (the next time point at which ECGs were performed).

4.8 Overdose

In clinical trials, nine patients received double the cumulative intended dose Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets. The safety profile of these patients did not differ from that of patients receiving the recommended dose, with no patient reporting SAEs.
In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTC interval prolongation

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Anti-malarial (P. falciparum malaria)
ATC code: P01BE05 (Dihydroartemisinin), P01BX02 (Piperaquine Phosphate)

Dihydroartemisinin is able to reach high concentrations within the parasitized erythrocytes. Its endoperoxide bridge is thought to be essential for its antimalarial activity, causing free-radical damage to parasite membrane systems including:
•Inhibition of falciparum sarcoplasmic-endoplasmic reticulum calcium ATPase
•Interference with mitochondrial electron transport
•Interference with parasite transport proteins
•Disruption of parasite mitochondrial function
The exact mechanism of action of piperaquine is unknown, but it likely mirrors that of chloroquine, a close structural analogue. Chloroquine binds to toxic haeme (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step. Piperaquine is a bisquinoline, and this class has shown good antimalarial activity against chloroquine-resistant Plasmodium strains in vitro. The bulky bisquinolone structure may be important for activity against chloroquine- resistant strains, and may act through the following mechanisms:
•Inhibition of the transporters that efflux chloroquine from the parasite food vacuole
•Inhibition of haem-digestion pathway in the parasite food vacuole.
Resistance to piperaquine (when used as monotherapy) has been reported

5.2 Pharmacokinetic properties

Pharmacokinetic profiles of Dihydroartemisinin and piperaquine have been investigated in animal models and in different human populations (healthy volunteers, adult patients and paediatric patients).

Absorption

Very rapidly absorbed, Tmax being approximately 1-2 hrs after single and multiple dosing. In patients, mean Cmax (CV%) and AUCINF of artenimol (observed after the first dose of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets were 752 (47%) mg/ml and 2,002 (45 %) ng/ml*h, respectively.

Artenimol bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria per se has an effect on artenimol disposition. This may reflect malaria-associated impairment of hepatic function, causing an increase in artenimol bioavailability (reduction of first hepatic effect) without affecting its apparent elimination half-life, which is absorption rate limited. In healthy male volunteers under fasting conditions, mean Cmax and AUCINF of artenimol ranged between 180-252 ng/ml and 516-684 mg/ml*h, respectively.

The systemic exposure was slightly lower following the last dose of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets (lower than after the first dose by up to 15%). artenimol pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. artenimol systemic exposure on the last day of treatment was higher in females than in males, the difference being within 30%.

In healthy volunteers, artenimol exposure was increased by 43% when administered with a high fat/high calorie meal.

Piperaquine, a highly lipophilic compound, is slowly absorbed. In humans, piperaquine has a Tmax of approximately 5 hours following a single and repeated dose. In patients mean (CV%) Cmax and AUC0-24(observed after the first dose of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets were 179 (62%) mg/ml and 1,679 (47%) mg/ml*h, respectively. Due to its slow elimination, piperaquine accumulates in plasma after multiple doses with an accumulation factor of approximately 3. Piperaquine pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. On the other hand, on the last day of Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets treatment, the piperaquine maximum plasma concentration was higher in female than in male healthy volunteers, the difference being in the order of 30 to 50%.

In healthy volunteers, piperaquine exposure is increased approximately 3-fold when administered with a high fat/high calorie meal. This pharmacokinetic effect is accompanied by an increased effect on prolongation of the QT interval. Accordingly, Dihydroartemisinin 40 mg And Piperaquine 320 mg Tablets should be administered with water no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose.

Distribution

Both piperaquine and artenimol are highly bound to human plasma proteins: the protein binding observed in in vitro studies was 44-93% for artenimol and >99% for piperaquine. Moreover, from in vitro and in vivo data in animals, piperaquine and artenimol tend to accumulate in RBC.

Artenimol was observed to have a small volume of distribution in humans (0.8 l/kg; CV 35.5%). Pharmacokinetic parameters observed for piperaquine in humans indicate that this active substance has a large volume of distribution (730 l/kg; CV 37.5%).

Biotransformation

Principally converted to α- artenimol-β-glucuronide (α- artenimol-G). Studies in human liver microsomes showed that artenimol was metabolised by the UDP-glucuronosyltransferase (UGT1A9 and UGT2B7) to α- artenimol-G with no cytochrome P450-mediated metabolism.

In vitro drug-drug interaction studies revealed that artenimol is an inhibitor of CYP1A2; therefore, there is the potential for artenimol to increase plasma concentrations of CYP1A2 substrates . In vitro metabolism studies demonstrated that piperaquine is metabolised by human hepatocytes (approximately 85% of piperaquine remained after 2 hours incubation at 37°C). Piperaquine was mainly metabolised by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. Piperaquine was found to be an inhibitor of CYP3A4 (also in a time- dependent way) and to a lesser extent of CYP2C19, while it stimulated the activity of CYP2E1.

No effect on the metabolite profile of piperaquine in human hepatocytes was observed when piperaquine was co-incubated with artenimol. The piperaquine major metabolites were a carboxyl acid cleavage product, and a mono-N-oxidated product.

In human studies, piperaquine was found to be a mild inhibitor of CYP3A4 enzyme while potent inhibitors of CYP3A4 activity caused mild inhibition of piperaquine metabolism.

Elimination

The elimination half-life of artenimol is approximately 1 hour. The mean oral clearance for adult patients with malaria was 1.34 l/h/kg. The mean oral clearance was slightly higher for paediatric patients, however the differences were minor in magnitude (<20%). Artenimol is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding artenimol excretion in humans are scarce. However, it is reported in the literature that the excretion of unchanged active substance in human urine and faeces is negligible for artemisinin derivatives.

The elimination half-life of piperaquine is around 22 days for adult patients and around 20 days for paediatric patients. The mean oral clearance for adult patients with malaria was

2.09 l/h/kg, while in paediatric patients was 2.43 l/h/kg. Due to its long elimination half-life, piperaquine accumulates after multiple dosing.

Animal studies showed that radio labelled piperaquine is excreted by the biliary route, while urinary excretion is negligible.

5.1 Preclinical Safety Data

Literature data concerning chronic toxicity of piperaquine in dogs and monkeys indicate some hepatotoxicity and mild reversible depression of total white cell and neutrophil counts.

The most important nonclinical safety findings after repeated dosing were the infiltration of macrophages with intracytoplasmic basophilic granular material consistent with phospholipidosis and degenerative lesions in numerous organs and tissues. These adverse reactions were seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use. It is not known whether these toxic effects are reversible. Piperaquine did not induce malformation in rats and rabbits. In a perinatal and postnatal development study (segment III) in female rats treated with 80 mg/kg, some animals had a delay of delivery inducing mortality of the neonates. In females delivering normally the development, behaviour and growth of the surviving progeny was normal following exposure in utero or via milk. No reproduction toxicity studies have been performed with the combination of artenimol and piperaquine

Central nervous system (CNS) toxicity

There is potential for neurotoxicity of artemisinin derivatives in man and animals, which is strongly related to the dose, route and formulations of the different artenimol pro-drugs. In humans, the potential neurotoxicity of orally administered artenimol can be considered highly unlikely, given the rapid clearance of artenimol, and its short exposure (3 days of treatment for malaria patients). There was no evidence of artenimol-induced lesions in the specific nuclei in rats or dogs, even at lethal dose.

Cardiovascular toxicity

Effects on blood pressure and on PR and QRS duration were observed at high piperaquine doses. The most important potential cardiac effect was related to cardiac conduction.

In the hERG test, the IC50 was 0.15 µmol for piperaquine and 7.7 µmol for artenimol. The association of artenimol and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity

There are no phototoxicity concerns with artenimol, as it does not absorb in the range of 290-700 nm.

Piperaquine has an absorption maximum at 352 nm. Since piperaquine is present in the skin (about 9% in the non-pigmented rat and only 3% in the pigmented rat), slight phototoxic reactions (swelling and erythema) were observed 24 hours after oral treatment in mice exposed to UV radiation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Maize Starch
Dextrose
Hydroxypropylcellulose
Magnesium Stearate
Colloidal Anhydrous Silica
Cross carmellose Sodium
Crospovidone
Hydroxy propyl methyl cellulose
Titanium Dioxide
Colour Tartrazine Yellow
Poly Ethylene Glycol 4000
Purified Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at temperature below 30˚C.

6.5 Nature and contents of container

1 x 8 Blister Pack. 8 Tablets are packed in 1 Blister and such 1 blister is packed in 1 carton along with insert.

6.6 Special precautions for disposal and other handling

No Special Requirements

7. APPLICANT/MANUFACTURER

MARKETED BY:

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