DOSSIER FOR REGISTRATION

OF

LOMASYL FORTE

(ARTEMETHER 80MG + LUMEFANTRINE 480MG TABLETS)

SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC)

SUBMITTED BY

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CHINA

1. NAME OF THE MEDICINAL PRODUCT

Name of the medicinal product(s): LOMASYL FORTE

Pharmaceutical form(s) and strength(s): Artemether 80mg + Lumefantrine 480mg tablets

INN/active Pharmaceutical ingredient(s): Artemether, Lumefantrine

ATC Code(s): P01BF01

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Quantity for unit content:

INGREDIENTS	SPECIFICATION	COMPOSITION	PURPOSE OF USE
Artemether	Ph.Int	80mg	Active ingredient
Lumefantrine	Ph.Int	480mg	Active ingredient
Starch Dextrin Sodium Starch Glycolate	BP BP USP	85 mg 45 mg 65 mg	Pharmaceutical aid Pharmaceutical aid Disintegrates

3. PHARMACEUTICAL FORM

Tables.

4. Clinical particulars

4.1 Therapeutic indications

Lomasyl Forte 80mg + 480mg tablet is indicated in treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* in patients of 5 kg bodyweight and above. Lomasyl Forte tablets have been shown to be effective in geographical regions where resistance to chloroquine has been reported [see Clinical Studies].

Limitations Of Use

- Lomasyl Forte tablets are not approved for patients with severe or complicated *P. falciparum* malaria.
- Lomasyl Forte tablets are not approved for the prevention of malaria.

4.2 Posology and method of administration

Lomasyl Forte tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

For patients who are unable to swallow the tablets such as infants and children, Lomasyl Forte tablets may be crushed and mixed with a small amount of water (1 to 2 teaspoons) in a clean container for administration immediately prior to use. The container can be rinsed with more water and the contents swallowed by the patient. The crushed tablet preparation should be followed whenever possible by food/drink (e.g., milk, formula, pudding, broth, and porridge).

In the event of vomiting within 1 to 2 hours of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarialfor treatment.

Dosage In Adult Patients (Greater Than 16 Years Of Age)

A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above:

Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice-daily (morning and evening) for the following 2 days (total course of 24 tablets).

For patients weighing less than 35 kg, see Dosage In Pediatric Patients.

Dosage In Pediatric Patients

A 3-day treatment schedule with a total of 6 doses is recommended as below:

5 kg To Less Than 15 kg Bodyweight

One tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice-daily (morning and evening) for the following 2 days (total course of 6 tablets).

15 kg To Less Than 25 kg Bodyweight

Two tablets as an initial dose, 2 tablets again after 8 hours and then 2 tablets twice-daily (morning and evening) for the following 2 days (total course of 12 tablets).

25 kg To Less Than 35 kg Bodyweight

Three tablets as an initial dose, 3 tablets again after 8 hours and then 3 tablets twice-daily (morning and evening) for the following 2 days (total course of 18 tablets).

35 kg Bodyweight And Above

Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice-daily (morning and evening) for the following 2 days (total course of 24 tablets).

Dosage In Patients With Hepatic Or Renal Impairment

No specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. Most patients with acute malaria present with some degree of related hepatic and/or renal impairment. In clinical studies, the adverse event profile did not differ in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. No specific dose adjustments are needed for patients with mild or moderate hepatic impairment.

In clinical studies, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function. There were few patients with severe renal impairment in clinical studies. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin (DHA) in healthy volunteers and while clinical experience in this population is limited, no dose adjustment is recommended.

Caution should be exercised when administering Lomasyl Forte tablets in patients with severe hepatic or renal impairment [see WARNINGS AND PRECAUTIONS].

4.3 Contraindications

Hypersensitivity

Known hypersensitivity to artemether, lumefantrine, or to any of the excipients of Lomasyl Forte tablets [see ADVERSE REACTIONS].

Strong CYP3A4 Inducers

Coadministration of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort with Lomasyl Forte tablets can result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy [see WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, and CLINICAL PHARMACOLOGY].

4.4 Special warnings and precautions for use

WARNINGS

Included as part of the "PRECAUTIONS" Section

PRECAUTIONS

Prolongation Of The QT Interval

Some antimalarials (e.g., halofantrine, quinine, quinidine) including Lomasyl Forte tablets have been associated with prolongation of the QT interval on the electrocardiogram.

Lomasyl Forte tablets should be avoided in patients:

- with congenital prolongation of the QT interval (e.g., long QT syndrome) or any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.
- with a family history of congenital prolongation of the QT interval or sudden death.
- with known disturbances of electrolyte balance, e.g., hypokalemia or hypomagnesemia.
- receiving other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolideantibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents) [see CLINICAL PHARMACOLOGY].
- receiving medications that are metabolized by the cytochrome enzyme CYP2D6 which also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see Drug Interactions With CYP2D6, DRUG INTERACTIONS, and CLINICAL PHARMACOLOGY].

Use Of QT Prolonging Drugs And Other Antimalarials

Halofantrine and Lomasyl Forte tablets should not be administered within 1 month of each other due to the long elimination half-life of lumefantrine (3 to 6 days) and potential additive effects on the QT interval [see Prolongation Of The QT Interval and CLINICAL PHARMACOLOGY].

Antimalarials should not be given concomitantly with Lomasyl Forte tablets, unless there is no other treatment option, due to limited safety data.

Drugs that prolong the QT interval, including antimalarials such as quinine and quinidine, should be used cautiously following Lomasyl Forte tablets, due to the long elimination half-life of lumefantrine (3

to 6 days) and the potential for additive effects on the QT interval; ECGmonitoring is advised if use of drugs that prolong the QT interval is medically required [see Prolongation Of The QT Interval, DRUG INTERACTIONS, and CLINICAL PHARMACOLOGY].

If mefloquine is administered immediately prior to Lomasyl Forte tablets there may be a decreased exposure to lumefantrine, possibly due to a mefloquine-induced decrease in bileproduction. Therefore, patients should be monitored for decreased efficacy and food consumption should be encouraged while taking Lomasyl Forte tablets [see DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS, and CLINICAL PHARMACOLOGY].

Drug Interactions With CYP3A4

When Lomasyl Forte tablets are coadministered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. When Lomasyl Forte tablets are coadministered with an inhibitor of CYP3A4, including grapefruit juice it may result in increased concentrations of artemether and/or lumefantrine and potentiate QT prolongation. When Lomasyl Forte tablets are coadministered with inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy
[see CONTRAINDICATIONS and DRUG INTERACTIONS].

Drugs that have a mixed effect on CYP3A4, especially antiretroviral drugs such as HIVprotease inhibitors and non-nucleoside reverse transcriptase inhibitors, and those that have an effect on the QT interval should be used with caution in patients taking Lomasyl Forte tablets [see DRUG INTERACTIONS].

Lomasyl Forte tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional nonhormonal method of birth control [see DRUG INTERACTIONS].

Drug Interactions With CYP2D6

Administration of Lomasyl Forte tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the coadministered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Lomasyl Forte tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see Prolongation Of The QT Interval, DRUG INTERACTIONS, and CLINICAL PHARMACOLOGY].

Recrudescence

Food enhances absorption of artemether and lumefantrine following administration of Lomasyl Forte tablets. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater [see DOSAGE AND ADMINISTRATION].

In the event of recrudescent *P. falciparum* infection after treatment with Lomasyl Forte tablets, patients should be treated with a different antimalarial drug.

Hepatic And Renal Impairment

Lomasyl Forte tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment [see DOSAGE AND ADMINISTRATION].

Plasmodium Vivax Infection

Lomasyl Forte tablets have been shown in limited data (43 patients) to be effective in treating the erythrocytic stage of *P. vivax* infection. However, relapsing malaria caused by *P. vivax*requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoites forms that may remain dormant in the liver.

Patient Counseling Information

Advise patients to read the FDA-Approved Patient Labeling (PATIENT INFORMATION).

Information for Safe Use

- Instruct patients to take Lomasyl Forte tablets with food. Patients who do not have an adequate intake of food are at risk for recrudescence of malaria.
- Patients with known hypersensitivity to artemether, lumefantrine, or to any of the excipients should not receive Lomasyl Forte tablets.
- Instruct patients to inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia.
- Instruct patients to inform their physician if they are taking any other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents).
- Instruct patients to notify their physicians if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.
- Instruct patients to avoid medications that are metabolized by the cytochrome enzyme CYP2D6 while receiving Lomasyl Forte tablets since these drugs also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine).

- Inform patients that based on animal data, Lomasyl Forte tablets administered during pregnancy may result in fetal loss. Fetal defects have been reported when artemisinins are administered to animals.
- Halofantrine and Lomasyl Forte tablets should not be administered within 1 month of each other due to potential additive effects on the QT interval.
- Antimalarials should not be given concomitantly with Lomasyl Forte tablets, unless there is no other treatment option, due to limited safety data.
- QT prolonging drugs, including quinine and quinidine, should be used cautiously following Lomasyl Forte tablets due to the long elimination half-life of lumefantrine and the potential for additive effects on the QT interval. ECG monitoring is advised if use of drugs that prolong the QT interval is medically required.
- Closely monitor food intake in patients who received mefloquine immediately prior to treatment with Lomasyl Forte tablets.
- Use Lomasyl Forte tablets cautiously in patients receiving other drugs that are substrates, inhibitors or inducers of CYP3A4, including grapefruit juice, especially those that prolong the QT interval or are antiretroviral drugs.
- Coadministration of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort is contraindicated with Lomasyl Forte tablets.
- Lomasyl Forte tablets may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional nonhormonal method of birth control.
- Inform patients that Lomasyl Forte tablets can cause hypersensitivity reactions. Instruct patients to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Carcinogenesis

Carcinogenicity studies were not conducted.

Mutagenesis

No evidence of mutagenicity was detected. The artemether: lumefantrine combination was evaluated using the *Salmonella* and *Escherichia*/mammalian-microsome mutagenicity test, the gene mutation test with Chinese hamster cells V79, the cytogenetic test on Chinese hamster cells *in vitro*, and the rat micronucleus test, *in vivo*.

Impairment Of Fertility

Pregnancy rates were reduced by about one-half in female rats dosed for 2 to 4 weeks with the artemetherlumefantrine combination at 1000 mg/kg (about 9 times the clinical dose based on body surface area comparisons). Male rats dosed for 70 days showed increases in abnormal sperm (87% abnormal) and increased testes weights at 30 mg/kg doses (about one-third the clinical dose). Higher doses (about 9 times the clinical dose) resulted in decreased sperm motility and 100% abnormal sperm cells.

Use In Specific Populations

Pediatric Use

The safety and effectiveness of Lomasyl Forte tablets have been established for the treatment of acute, uncomplicated malaria in studies involving pediatric patients weighing 5 kg or more [see Clinical Studies]. The safety and efficacy have not been established in pediatric patients who weigh less than 5 kg. Children from non-endemic countries were not included in clinical trials.

Geriatric Use

Clinical studies of Lomasyl Forte tablets did not include sufficient numbers of subjects aged 65 years and over to determine they respond differently from younger subjects. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Lomasyl Forte tablets.

Hepatic And Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. Lomasyl Forte tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and DHA, no dose adjustment for the use of Lomasyl Forte tablets in patients with renal impairment is advised. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment [see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS].

4.5 Interaction with other medicinal products and other forms of interaction

Rifampin

Oral administration of rifampin, a strong CYP3A4 inducer, with Lomasyl Forte tablets resulted in significant decreases in exposure to artemether, dihydroartemisinin (DHA, metabolite of artemether) and lumefantrine by 89%, 85% and 68%, respectively, when compared to exposure values after Lomasyl Forte tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort is contraindicated with Lomasyl Forte tablets [see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY].

Ketoconazole

Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of Lomasyl Forte tablets resulted in a moderate increase in exposure to artemether, DHA, and lumefantrine in a study of 15 healthy subjects. No dose adjustment of Lomasyl Forte tablets is necessary when administered with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Lomasyl Forte tablets should be used cautiously with drugs that inhibit CYP3A4 [see WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY].

Antiretroviral Drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Antiretroviral drugs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Therefore, the effects of antiretroviral drugs on the exposure to artemether, DHA, and lumefantrine are also variable [see CLINICAL PHARMACOLOGY]. Lomasyl Forte tablets should be used cautiously in patients on antiretroviral drugs because decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Lomasyl Forte tablets, and increased lumefantrine concentrations may cause QT prolongation [see WARNINGS AND PRECAUTIONS].

Prior Use Of Mefloquine

Administration of 3 doses of mefloquine followed 12 hours later by a 6-dose regimen of Lomasyl Forte tablets in 14 healthy volunteers demonstrated no effect of mefloquine on plasma concentrations of artemether or the artemether/DHA ratio. However, exposure to lumefantrine was reduced, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be monitored for decreased efficacy and food consumption should be encouraged with administration of Lomasyl Forte tablets [see WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY].

Hormonal Contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Lomasyl Forte tablets may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control [see WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY].

CYP2D6 Substrates

Lumefantrine inhibits CYP2D6 *in vitro*. Administration of Lomasyl Forte tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the coadministered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Lomasyl Forte tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY].

Sequential Use Of Quinine

A single dose of intravenous quinine (10 mg/kg bodyweight) concurrent with the final dose of a 6-dose regimen of Lomasyl Forte tablets demonstrated no effect of intravenous quinine on the systemic exposure of DHA or lumefantrine. Quinine exposure was also not altered. Exposure to artemether was decreased. This decrease in artemether exposure is not thought to be clinically significant. However, quinine and other drugs that prolong the QT interval should be used cautiously following treatment with Lomasyl Forte tablets due to the long elimination half-life of lumefantrine and the potential for additive QT effects; ECGmonitoring is advised if use of drugs that prolong the QT interval is medically required [see WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY].

Interaction With Drugs That Are Known To Prolong The QT Interval

Lomasyl Forte tablets are to be used with caution when coadministered with drugs that may cause prolonged QT interval such as antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents [see WARNINGS AND PRECAUTIONS].

4.6 Pregnancy and Lactation

Pregnancy

Pregnancy Category C

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Lomasyl Forte tablets (including a third of patients who were exposed in the first trimester), and published data of over 1,000 pregnant patients who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rate.

The efficacy of Lomasyl Forte tablets in the treatment of acute, uncomplicated malaria in pregnant women has not been established.

Lomasyl Forte tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant rats dosed during the period of organogenesis at or higher than a dose of about half the highest clinical dose of 1120 mg artemether-lumefantrine per day (based on body surface area comparisons), showed increases in fetal loss, early resorptions and post implantation loss. No adverse effects were observed in animals dosed at about one-third the highest clinical dose. Similarly, dosing in pregnant rabbits at about 3 times the clinical dose (based on body surface area comparisons) resulted in abortions, preimplantation loss, post implantation loss and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at 2 times the clinical dose. Embryo-fetal loss is a significant reproductive toxicity. Other artemisinins are known to be embryotoxic in animals. However, because metabolic profiles in animals and humans are dissimilar, artemether exposures in animals may not be predictive of human exposures [see Nonclinical Toxicology]. These data cannot rule out an increased risk for early pregnancy loss or fetal defects in humans.

Nursing Mothers

It is not known whether artemether or lumefantrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lomasyl Forte tablets are administered to a nursing woman. Animal data suggest both artemether and lumefantrine are excreted into breast milk. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to artemether and lumefantrine through breast milk.

4.7 Effects on ability to drive and use machines

Lomasyl Forte 80mg + 480mg tablet has no influence on the ability to drive and use machines.

4.8 Undesirable effects

No case of undesirable effects has been reported.

4.9 Overdose

There is no information on overdoses of Lomasyl Forte tablets higher than the doses recommended for treatment.

In cases of suspected overdosage, symptomatic and supportive therapy, which would include ECG and blood electrolyte monitoring, should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Mechanism of Action

Lomasyl Forte tablets, a fixed dose combination of artemether and lumefantrine in the ratio of 1:6, is an antimalarial agent [see Microbiology (12.4)].

5.2 Pharmacokinetic properties

Pharmacokinetics

Absorption

Following administration of Lomasyl Forte tablets to healthy volunteers and patients with malaria, artemether is absorbed with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentrations about 6 to 8 hours after administration. The single dose (4 tablets) pharmacokinetic parameters for artemether, DHA, an active antimalarial metabolite of artemether, and lumefantrine in adult Caucasian healthy volunteers are given in Table 3. Multiple dose data after the 6-dose regimen of Lomasyl Forte tablets in adult malaria patients are given in Table 4.

Table 3: Single Dose Pharmacokinetic Parametersa for Artemether, Dihydroartemisinin, and Lumefantrine Under-Fed Conditions
Abbreviations: DHA, dihydroartemisinin; SD, standard deviation; AUC, area under the curve. aMean ± SD

Cmax, AUClast, t½ and Median Tmax.		
	Study 2102 (n = 50)	Study 2104 (n = 48)
Artemether		
Cmax (ng/mL)	60.0 ± 32.5	83.8 ± 59.7
Tmax (h)	1.50	2.00
AUClast (ng·h/mL)	146 ± 72.2	259 ± 150
t½ (h)	1.6 ± 0.7	2.2 ± 1.9
DHA		
Cmax (ng/mL)	104 ± 35.3	90.4 ± 48.9
Tmax (h)	1.76	2.00
AUClast (ng·h/mL)	284 ± 83.8	285 ± 98.0
t½ (h)	1.6 ± 0.6	2.2 ± 1.5
Lumefantrine		
Cmax (µg/mL)	7.38 ± 3.19	9.80 ± 4.20
Tmax (h)	6.01	8.00
AUClast (µg·h/mL)	158 ± 70.1	243 ± 117
t½ (h)	101 ± 35.6	119 ± 51.0

Food enhances the absorption of both artemether and lumefantrine. In healthy volunteers, the relative bioavailability of artemether was increased between 2- to 3-fold, and that of lumefantrine 16-fold when Lomasyl Forte tablets were taken after a high-fat meal compared under fasted conditions. Patients should be encouraged to take Lomasyl Forte tablets with a meal as soon as food can be tolerated [see Dosage and Administration (2.1)].

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin (DHA) is also bound to human serum proteins (47% to 76%). Protein binding to human plasma proteins is linear.

Biotransformation

In human liver microsomes and recombinant CYP450 enzymes, the metabolism of artemether was catalyzed predominantly by CYP3A4/5. Dihydroartemisinin (DHA) is an active metabolite of artemether. The metabolism of artemether was also catalyzed to a lesser extent by CYP2B6, CYP2C9 and CYP2C19. In vitro studies with artemether at therapeutic concentrations revealed no significant inhibition of the metabolic activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11. In vitro studies with artemether, DHA, and lumefantrine at therapeutic concentrations revealed no significant induction of the metabolic activities of CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, or CYP3A5.

During repeated administration of Lomasyl Forte tablets, systemic exposure of artemether decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. The artemether/DHA area under the curve (AUC) ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. This suggests that there was induction of enzymes responsible for the metabolism of artemether.

In human liver microsomes and in recombinant CYP450 enzymes, lumefantrine was metabolized mainly by CYP3A4 to desbutyl-lumefantrine. The systemic exposure to the metabolite desbutyl-lumefantrine was less than 1% of the exposure to the parent compound. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Caution is recommended when combining Lomasyl Forte tablets with substrates, inhibitors, or inducers of CYP3A4, especially antiretroviral drugs and those that prolong the QT interval (e.g., macrolide antibiotics, pimozide) [see Contraindications (4), Warnings and Precautions (5.1, 5.2, 5.3), and Drug Interactions (7)].

Coadministration of Lomasyl Forte tablets with CYP2D6 substrates may result in increased plasma concentrations of the CYP2D6 substrate and increase the risk of adverse reactions. In addition, many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Lomasyl Forte tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine) [see Warnings and Precautions (5.1, 5.4) and Drug Interactions (7.6)].

Elimination

Artemether and DHA are cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with an elimination half-life of 3 to 6 days in healthy volunteers and in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether and lumefantrine.

In 16 healthy volunteers, neither lumefantrine nor artemether was found in the urine after administration of Lomasyl Forte tablets, and urinary excretion of DHA amounted to less than 0.01% of the artemether dose.

Specific Populations

Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. There is no significant renal excretion of lumefantrine, artemether, and DHA in healthy volunteers and while clinical experience in this population is limited, no dose adjustment in renal impairment is recommended [see Dosage and Administration (2.4)].

Pediatric Patients

The PK of artemether, DHA, and lumefantrine were obtained in 2 pediatric studies by sparse sampling using a population-based approach. PK estimates derived from a composite plasma concentration profile for artemether, DHA, and lumefantrine are provided in Table 4.

Systemic exposure to artemether, DHA, and lumefantrine, when dosed on an mg/kg body weight basis in pediatric patients (greater than or equal to 5 to less than 35 kg body weight), is comparable to that of the recommended dosing regimen in adult patients.

Table 4: Summary of Pharmacokinetic Parameters for Lumefantrine, Artemether, and DHA in Pediatric and Adult Patients With Malaria Following Administration of a 6-dose Regimen of Lomasyl Forte tablets

	Adults1	Pediatric Patients (body weight, kg)2		
Drug		5 to < 15	15 to < 25	25 to < 35
Lumefantrine				
Mean Cmax, range (mcg/mL)	5.60-9.0	4.71–12.6		Not Available
Mean AUClast, range (mcg·h/mL)	410-561	372–699		Not Available
Artemether				
Mean Cmax ± SD (ng/mL)	186 ± 125	223 ± 309	198 ± 179	174 ± 145
Dihydroartemisinin				
Mean Cmax ± SD (ng/mL)	101 ± 58	54.7 ± 58.9	79.8 ± 80.5	65.3 ± 23.6

Abbreviations: AUC, area under the curve; DHA, dihydroartemisinin; SD, standard deviation.
1There are a total of 181 adults for lumefantrine pharmacokinetic parameters and a total of 25 adults for artemether and dihydroartemisinin pharmacokinetic parameters.
2There are 477 children for the lumefantrine pharmacokinetic parameters; for artemether and dihydroartemisinin pharmacokinetic parameters there are 55, 29, and 8 children
for the 5 to less than 15, 15 to less than 25 and the 25 to less than 35 kg groups, respectively.

Geriatric Patients

No specific pharmacokinetic studies have been performed in patients older than 65 years of age.

Drug Interaction Studies

Rifampin (strong CYP3A4 inducer)

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Lomasyl Forte tablets (6-dose regimen over 3 days) in 6 HIV-1 and tuberculosis co-infected adults without malaria resulted in significant decreases in exposure, in terms of AUC, to artemether, DHA and lumefantrine by 89%, 85%, and 68%, respectively, when compared to exposure values after Lomasyl Forte tablets alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort is contraindicated with Lomasyl Forte tablets [see Contraindications (4)].

Ketoconazole (potent CYP3A4 inhibitor)

Concurrent oral administration of ketoconazole (400 mg on day 1 followed by 200 mg on Days 2, 3, 4, and 5) with Lomasyl Forte tablets (single-dose of 4 tablets of 20 mg artemether/120 mg lumefantrine per tablet) with a meal led to an increase in exposure, in terms of AUC, of artemether (2.3-fold), DHA (1.5-fold), and lumefantrine (1.6-fold) in 13 healthy subjects. The pharmacokinetics of ketoconazole was not evaluated. Based on this study, dose adjustment of Lomasyl Forte tablets is considered unnecessary when administered with ketoconazole or other CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine, which could lead to QT prolongation, Lomasyl Forte tablets should be used cautiously with other drugs that inhibit CYP3A4 (e.g., antiretroviral drugs, macrolide antibiotics, antidepressants, imidazole antifungal agents) [see Warnings and Precautions (5.1, 5.3)].

Antimalarials

The oral administration of mefloquine in 14 healthy volunteers administered as 3 doses of 500 mg, 250 mg, and 250 mg, followed 12 hours later by Lomasyl Forte tablets (6 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine per tablet), had no effect on plasma concentrations of artemether or the artemether/DHA ratio. In the same study, there was a 30% reduction in Cmax and 40% reduction in AUC of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production.

Intravenous administration of a single dose of quinine (10 mg/kg bodyweight) concurrent with the last dose of a 6-dose regimen of Lomasyl Forte tablets had no effect on systemic exposure of DHA, lumefantrine, or quinine in 14 healthy volunteers. Mean AUC of artemether were 46% lower when administered with quinine compared to Lomasyl Forte tablets alone. This decrease in artemether exposure is not thought to be clinically significant. However, quinine should be used cautiously in patients following treatment with Lomasyl Forte tablets due to the long elimination half-life of lumefantrine and the potential for additive effects on the QT interval; ECG monitoring is advised if use of quinine is medically required [see Warnings and Precautions (5.2)].

Antiretroviral Drugs

The oral administration of lopinavir/ritonavir (400 mg/100 mg twice daily for 26 days) in 10 healthy volunteers coadministered with Lomasyl Forte tablets (6-dose regimen over 3 days), resulted in a decrease in systemic exposures, in terms of AUC, to artemether and DHA by approximately 40%, but an increase in exposure to lumefantrine by approximately 2.3-fold. The oral administration of efavirenz (600 mg once daily for 26 days) in 12 healthy volunteers coadministered with Lomasyl Forte tablets (6-dose regimen over 3 days), resulted in a decrease in exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to lopinavir/ritonavir and efavirenz were not significantly affected by concomitant use of Lomasyl Forte tablets. Lomasyl Forte tablets should be used cautiously in patients on antiretroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors because decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Lomasyl Forte tablets, and increased lumefantrine concentrations may cause QT prolongation [see Warnings and Precautions (5.3) and Drug Interactions (7.3)].

Hormonal Contraceptives

No clinical drug-drug interaction studies between Lomasyl Forte tablets and hormonal contraceptives have been performed. In vitro studies revealed that the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A4. Therefore, coadministration of Lomasyl Forte tablets may potentially reduce the effectiveness of hormonal contraceptives [see Warnings and Precautions (5.3) and Drug Interactions (7.5)].

Microbiology

Mechanism of Action

Lomasyl Forte tablets, a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively, is an antimalarial agent. Artemether is rapidly metabolized into an active metabolite DHA. The antimalarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine exerts its antimalarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of β-hematin by forming a complex with hemin. Both artemether and lumefantrine were shown to inhibit nucleic acid and protein synthesis.

Activity In Vitro and In Vivo

Artemether and lumefantrine are active against the erythrocytic stages of P. falciparum.

Drug Resistance

There is a potential for development of resistance to artemether and lumefantrine. Strains of P. falciparum with a moderate decrease in susceptibility to artemether or lumefantrine alone can be selected in vitro or in vivo, but not maintained in the case of artemether. Alterations in some genetic regions of P. falciparum [multidrug resistant 1 (pfmdr1), chloroquine resistance transporter (pfcrt), and kelch 13 (K13)] based on in vitro testing and/or identification of isolates in endemic areas where artemether/lumefantrine treatment was administered, have been reported. The clinical relevance of these findings are not known.

Effects on the Electrocardiogram

In a healthy adult volunteer parallel-group study including a placebo and moxifloxacin control-group (n = 42 per group), the administration of the 6-dose regimen of Lomasyl Forte tablets was associated with prolongation of QTcF (Fridericia). Following administration of a 6-dose regimen of Lomasyl Forte tablets consisting of 4 tablets per dose (total of 4 tablets of 80 mg artemether/480 mg lumefantrine) taken with food, the maximum mean change from baseline and placebo adjusted QTcF was 7.5 msec (1-sided 95% upper confidence interval: 11 msec). There was a concentration-dependent increase in QTcF for lumefantrine.

In clinical trials conducted in children, no patient had QTcF greater than 500 msec. Over 5% of patients had an increase in QTcF of over 60 msec.

In clinical trials conducted in adults, QTcF prolongation of greater than 500 msec was reported in 3 (0.3%) patients. Over 6% of adults had a QTcF increase of over 60 msec from baseline.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were not conducted.

Mutagenesis

No evidence of mutagenicity was detected. The artemether-lumefantrine combination was evaluated using the Salmonella and Escherichia/mammalian-microsome mutagenicity test, the gene mutation test with Chinese hamster cells V79, the cytogenetic test on Chinese hamster cells in vitro, and the rat micronucleus test, in vivo.

Impairment of Fertility

Pregnancy rates were reduced by about one-half in female rats dosed for 2 to 4 weeks with the artemether-lumefantrine combination at 1000 mg/kg (about 9 times the clinical dose based on BSA

comparisons). Male rats dosed for 89 to 93 days showed increases in abnormal sperm (87% abnormal) at 30 mg/kg doses (about one-third the clinical dose). Higher doses (about 9 times the MRHD) resulted in increased testes weights, decreased sperm motility, and 100% abnormal sperm cells.

Animal Toxicology and/or Pharmacology

Neonatal rats (7 to 21 days old) were more sensitive to the toxic effects of artemether (a component of Lomasyl Forte tablets) than older juvenile rats or adults. Mortality and severe clinical signs were observed in neonatal rats at doses which were well tolerated in pups above 22 days old.

CLINICAL STUDIES

Treatment of Acute, Uncomplicated P. falciparum Malaria

The efficacy of Lomasyl Forte tablets was evaluated for the treatment of acute, uncomplicated malaria caused by P. falciparum in HIV negative patients in 8 clinical studies. Uncomplicated malaria was defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction. Baseline parasite density ranged from 500/mcL to 200,000/mcL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in partially immune and non-immune adults and children (greater than or equal to 5 kg body weight) with uncomplicated malaria in China, Thailand, sub-Saharan Africa, Europe, and South America. Patients who had clinical features of severe malaria, severe cardiac, renal, or hepatic impairment were excluded.

The studies include two 4-dose studies assessing the efficacy of the components of the regimen, a study comparing a 4-dose versus a 6-dose regimen, and 5 additional 6-dose regimen studies.

Lomasyl Forte tablets were administered at 0, 8, 24, and 48 hours in the 4-dose regimen, and at 0, 8, 24, 36, 48, and 60 hours in the 6-dose regimen. Efficacy endpoints consisted of:

- 28-day cure rate, defined as clearance of asexual parasites (the erythrocytic stage) within 7 days without recrudescence by Day 28
- parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours
- fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature greater than 37.5°C at baseline)

The modified intent-to-treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least 1 dose of study drug. Evaluable patients generally are all patients who had a Day 7 and a Day 28 parasitological assessment or experienced treatment failure by Day 28.

Studies 1 and 2: The 2 studies, which assessed the efficacy of Lomasyl Forte tablets (4 doses of 4 tablets of 20 mg artemether/120 mg lumefantrine) compared to each component alone, were randomized, double-blind, comparative, single center, conducted in China. The efficacy results (Table 5) support that the combination of artemether and lumefantrine in Lomasyl Forte tablets had a significantly higher 28-day cure rate compared to artemether and had a significantly faster PCT and FCT compared to lumefantrine.

Table 5: Clinical Efficacy of Lomasyl Forte tablets Versus Components (mITT Population)1

Study No. Region/patient ages	28-day cure rate2 n/N (%) patients	Median FCT3 [25th, 75th percentile]	Median PCT [25th, 75th percentile]
Study 1 China, ages 13 to 57 years			
Lomasyl Forte tablets	50/51 (98.0)	24 hours [9, 48]	30 hours [24, 36]
Artemether4	24/52 (46.2)	21 hours [12, 30]	30 hours [24, 33]
Lumefantrine5	47/52 (90.4)	60 hours [36, 78]	54 hours [45, 66]
Study 2 China, ages 12 to 65 years			
Lomasyl Forte tablets	50/52 (96.2)	21 hours [6, 33]	30 hours [24, 36]
Lumefantrine6	45/51 (88.2)	36 hours [12, 60]	48 hours [42, 60]

Abbreviations: FCT, fever clearance time; mITT, modified intent-to-treat; PCT, parasite clearance time.
1In mITT analysis, patients whose status was uncertain were classified as treatment failures.
2Efficacy cure rate based on blood smear microscopy.
3For patients who had a body temperature greater than 37.5°C at baseline only.
495% Confidence Interval (Lomasyl Forte tablets–artemether) on 28-day cure rate: 37.8%, 66.0%.
5P-value comparing Lomasyl Forte tablets to lumefantrine on PCT and FCT: < 0.001.
6P-value comparing Lomasyl Forte tablets to lumefantrine on PCT: < 0.001 and on FCT: < 0.05.

Results of 4-dose studies conducted in areas with high resistance such as Thailand during 1995-96 showed lower efficacy results than the above studies. Therefore, Study 3 was conducted.

Study 3: Study 3 was a randomized, double-blind, 2-center study conducted in Thailand in adults and children (aged greater than or equal to 2 years), which compared the 4-dose regimen (administered over 48 hours) of Lomasyl Forte tablets to a 6-dose regimen (administered over 60 hours). Twenty-eight day cure rate in mITT subjects was 81% (96/118) for the Lomasyl Forte tablets 6-dose arm as compared to 71% (85/120) in the 4-dose arm.

Studies 4, 5, 6, 7, and 8: In these studies, Lomasyl Forte tablets were administered as the 6-dose regimen.

In study 4, a total of 150 adults and children aged greater than or equal to 2 years received Lomasyl Forte tablets. In study 5, a total 164 adults and children greater than or equal to 12 years received Lomasyl Forte tablets. Both studies were conducted in Thailand.

Study 6 was a study of 165 non-immune adults residing in regions non-endemic for malaria (Europe and Colombia) who contracted acute uncomplicated P. falciparum malaria when traveling in endemic regions.

Study 7 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature greater than or equal to 37.5ºC.

Study 8 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to less than 35 kg, with fever (greater than or equal to 37.5°C axillary or greater than or equal to 38°C rectally) or history of fever in the preceding 24 hours.

Results of 28-day cure rate, median PCT, and FCT for Studies 3 to 8 are reported in Table 6.

Table 6: Clinical Efficacy of 6-dose Regimen of Lomasyl Forte tablets

Study No. Region/ages	28-day cure rate1 n/N (%) Patients		Median FCT2 [25th, 75thpercentile]	Median PCT [25th, 75thpercentile]
	mITT3	Evaluable		
Study 3 Thailand, ages 3–62 years	96/118 (81.4)	93/96 (96.9)	35 hours [20, 46]	44 hours [22, 47]
Early failure4	0	0		
Late failure5	4 (3.4)	3 (3.1)		
Lost to follow-up	18 (15.3)			
Other6	0			
Study 4 Thailand, ages 2–63 years	130/149 (87.2)	130/134 (97.0)	22 hours [19, 44]	NA
Early failure4	0	0		
Late failure5	4 (2.7)	4 (3.0)		
Lost to follow-up	13 (8.7)			
Other6	2 (1.3)			

Study 5 Thailand, ages 12–71 years	148/164 (90.2)	148/155 (95.5)	29 hours [8, 51]	29 hours [18, 40]
Early failure4	0	0		
Late failure5	7 (4.3)	7 (4.5)		
Lost to follow-up	9 (5.5)			
Other6	0			
Study 6 Europe/Columbia, ages 16–66 years	120/162 (74.1)	119/124 (96.0)	37 hours [18, 44]	42 hours [34, 63]
Early failure4	6 (3.7)	1 (0.8)		
Late failure5	3 (1.9)	3 (2.4)		
Lost to follow-up	17 (10.5)			
Other6	16 (9.9)	1 (0.8)		
Study 7 Africa, ages 2 months–9 years	268/310 (86.5)	267/300 (89.0)	8 hours [8, 24]	24 hours [24, 36]
Early failure4	2 (0.6)	0		
Late failure5	34 (11.0)	33 (11.0)		
Lost to follow-up	2 (0.6)			
Other6	4 (1.3)			
Study 8 Africa, ages 3 months–12 years	374/452 (82.7)	370/419 (88.3)	8 hours [8, 23]	35 hours [24, 36]
Early failure4	13 (2.9)	0		
Late failure5	49 (10.8)	49 (11.7)		
Lost to follow-up	6 (1.3)			
Other6	10 (2.2)			

Abbreviations: FCT, fever clearance time; mITT, modified intent-to-treat; PCT, parasite clearance time; NA, not applicable.
1Efficacy cure rate based on blood smear microscopy.
2For patients who had a body temperature greater than 37.5°C at baseline only.

3In mITT analysis, patients whose status was uncertain were classified as treatment failures.
4Early failures were usually defined as patients withdrawn for unsatisfactory therapeutic effect within the first 7 days or because they received another antimalarial medication within the first 7 days.
5Late failures were defined as patients achieving parasite clearance within 7 days but having parasite reappearance including recrudescence or new infection during the 28-day follow-up period.
6Other includes withdrawn due to protocol violation or non-compliance, received additional medication after day 7, withdrew consent, missing day 7 or 28 assessment.

In all studies, patients' signs and symptoms of malaria resolved when parasites were cleared.

In studies conducted in areas with high transmission rates, such as Africa, reappearance of P. falciparumparasites may be due to recrudescence or a new infection.

The efficacy by body weight category for studies 7 and 8 is summarized in Table 7.

Table 7: Clinical Efficacy by Weight for Pediatric Studies

Study No. Age category	Lomasyl Forte tablets 6-dose Regimen		
	mITT Population1		Evaluable Population
	Median PCT [25th, 75th percentile]	28-day cure rate2 n/N (%) patients	28-day cure rate2 n/N (%) patients
Study 7			
5 to < 10 kg	24 [24, 36]	133/154 (86.4)	133/149 (89.3)
10 to < 15 kg	35 [24, 36]	94/110 (85.5)	94/107 (87.9)
15 to 25 kg	24 [24, 36]	41/46 (89.1)	40/44 (90.9)
Study 83			
5 to < 10 kg	36 [24, 36]	61/83 (73.5)	61/69 (88.4)
10 to < 15 kg	35 [24, 36]	160/190 (84.2)	157/179 (87.7)
15 to < 25 kg	35 [24, 36]	123/145 (84.8)	123/140 (87.9)
25 to < 35 kg	26 [24, 36]	30/34 (88.2)	29/31 (93.5)

Abbreviations: mITT, modified intent-to-treat; PCT, parasite clearance time.
1In mITT analysis, patients whose status was uncertain were classified as treatment failures.
2Efficacy cure rate based on blood smear microscopy.

3Lomasyl Forte tablets administered as crushed tablets.

The efficacy of Lomasyl Forte tablets for the treatment P. falciparum infections mixed with P. vivax was assessed in a small number of patients. Lomasyl Forte tablets are only active against the erythrocytic phase of P. vivax malaria. Of the 43 patients with mixed infections at baseline, all cleared their parasitemia within 48 hours. However, parasite relapse occurred commonly (14/43; 33%). Relapsing malaria caused by P. vivax requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoite forms that may remain dormant in the liver.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Quantity for unit content:

INGREDIENTS	SPECIFICATION	COMPOSITION	PURPOSE OF USE
Starch	BP	85 mg	Pharmaceutical aid
Dextrin	BP	45 mg	Pharmaceutical aid
Sodium Starch Glycolate	USP	65 mg	Disintegrates

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30C°. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container <and special equipment for use, administration or implantation

6 tablets in one blister, one blister per box with leaflet, 200 boxes per carton.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. APPLICANT/MANUFACTURER

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