SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

NEWMARTEM FORTE (ARTEMETER 80 MG AND LUMEFANTRINE 480 MG TABLETS PH. INT.)

2. Qualitative and quantitative composition

Description: Yellow coloured, circular shaped, biconvex, film coated tablet having breakline on one side and plain on other side.

Composition:
Each film coated tablet contains:

Artemether Ph. Int. 80 mg

Lumefantrine Ph. Int. 480 mg

Colour: Approved colour used

Excipients: q.s.

Sr. No.	Name of Ingredient	Spec.	Qty. in mg/ Tab	Ovg.	Reason for Inclusion
1.	Lumefantrine	Ph. Int	480.000	--	Active
2.	Microcrystalline Cellulose	BP	20.000	--	Diluent
3.	Maize Starch	BP	24.000	--	Binder
4.	Maize Starch (Paste)	BP	11.000	--	Binder
5.	Polysorbate 80 (Tween 80)	BP	5.000	--	Solubilizer
6.	**Purified Water	Inhouse	Q.S.	--	Solvent
Lubrication					
7.	Artemether	Ph. Int.	80.000	--	Active
8.	Colloidal Anhydrous Silica	BP	6.000	--	Glidant
9.	Magnesium Stearate	BP	10.000	--	Lubricant
10.	Purified talc	BP	8.000	--	Glidant
11.	Croscarmellose sodium	BP	28.000	--	Disintegrant
12.	*Maize Starch (additional)	BP	3.500	--	Binder
	TOTAL		**672.00**		
Film Coating					
13.	Readycoat Quinoline Yellow Lake (32F0431432)	Inhouse	20.000	--	Coloring Agent
14.	**Isopropyl alcohol	BP	100.000	--	Solvent
15.	**Methylene Chloride	BP	200.000	--	Solvent
	TOTAL		**692.000**		

3. Pharmaceutical form

Film Coated Tablets

4. Clinical particulars

4.1 Therapeutic indications

Treatment of malaria caused by all forms of Plasmodium, including multiple drug resistant strains of P. Falciparum

4.2 Posology and method of administration

Posology

Route of Administration: Oral

As directed by the Physician.

Body Weight	Day - 1		Day - 2		Day - 3	
	0 Hrs	8 Hrs after	Morning	Evening	Morning	Evening
adult & children 35 kg & above	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet

Method of administration

It should be taken with food or milky drink. Patients who vomit within 1 hour of taking the medication should repeat the dose. For administration to small children and infants, the tablet/s may be crushed.

4.3 Contraindications

It is contraindicated in:

• Patients with known hypersensitivity to the active substances or to any of the excipients.

• Patients with severe malaria according to WHO definition.

• Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. metoprolol, imipramine, amitryptyline, clomipramine)

• Patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.

• Patients with a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

• Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

• Patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin

4.4 Special warnings and precautions for use

i) It must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

ii) Due to limited data on safety and efficacy, it should not be given concurrently with any other antimalarial

agent, unless there is no other treatment option.

iii) If a patient deteriorates whilst taking, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances.

iv) The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with this combination.

v) If quinine is given after this combination, close monitoring of the ECG is advised.

vi) If it is given after mefloquine, close monitoring of food intake is advised.

vii) In patients previously treated with halofantrine, it should not be administered earlier than one month after the last halofantrine dose.

viii) It is not indicated and has not been evaluated for prophylaxis.

ix) It should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of this tablet.

x) Like other antimalarials (e.g. halofantrine, quinine and quinidine) it has the potential to cause QT prolongation.

xi) Caution is recommended when combining with hormonal contraceptives. It may reduce the effectiveness of hormonal contraceptives.

xii) In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with drugs that are known to prolong the QTc interval

It is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval) such as antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics, macrolides, fluoroquinolones, imidazole, triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide

Interaction with other antimalarial drugs

Data on safety and efficacy are limited and it should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If it is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised.

In patients previously treated with halofantrine, it should not be administered earlier than one month after the last halofantrine dose.

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with this led to a modest increase (≤ 2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects.

Interaction with hormonal contraceptives

It may potentially reduce the effectiveness of hormonal contraceptives.

4.6 Pregnancy and lactation
There is insufficient data from the use of Artemether and Lumefantrine in pregnant women. There is no information on the effects of Artemether and Lumefantrine on human fertility.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Patients receiving Artemether and Lumefantrine Tablets should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.8 Undesirable effects
Common side effects include headache, dizziness, loss of appetite, weakness, fever, chills, tiredness, muscle or joint pain, nausea, vomiting, abdominal pain, cough, and trouble sleeping (insomnia)
Serious side effect such as:
• Worsening malaria symptoms
• Severe vomiting or loss of appetite
• Headache with chest pain and severe dizziness, fainting, fast or pounding heartbeats
• The first sign of any skin rash

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

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimalarials, blood schizonticide., ATC Code: P01BF01

Mechanism of action
Artemether and Lumefantrine 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 dihydroartemisinin (DHA). The anti- malarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine, exerts its anti-malarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of [3-hematin by forming a complex with hemin. Both artemether and lumefantrine were shown to inhibit nucleic acid and protein synthesis. Artemether and lumefantrine are active against the erythrocytic stages of Plasmodium falciparum.

5.2 Pharmacokinetic properties

Absorption

Artemether is absorbed fair1y rapidly and dihydroartemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUG values of artemether ranged between 60.0-104 ng/mL and 146-338 ng·h/mL, respectively, in fed healthy adults after a single dose of Artemether + Lumefantrine Tablet, 80 mg artemether/480 mg lumefantrine. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µg·h/mL. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when Artemether + Lumefantrine Tablet was taken after a high-fat meal.

Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions would be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin 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 Artemether/ Lumefantrine Tablets, systemic exposure of artemether decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. The artemether/DHAAUC 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.

Elimination

Artemether and □HA are cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with a terminal half-life of 3-6 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.

5.3 Preclinical safety data
Not Applicable

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose, Maize Starch, Polysorbate 80 (Tween 80), Purified Water, Colloidal Anhydrous Silica, Magnesium Stearate, Purified talc, Croscarmellose Sodium, Readycoat Quinoline Yellow Lake (32F0431432), Isopropyl Alcohol, Methylene Chloride.

6.2 Incompatibilities
None

6.3 Shelf life
36 months (3 years)

6.4 Special precautions for storage
Store protected from light & moisture at a temperature not exceeding 30°C
Keep medicines out of reach of children.

6.5 Nature and contents of container

Blister pack of 6 tablets.

6.6 Special precautions for disposal and other handling
No special requirement

7. Marketing authorisation holder
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8. Marketing authorisation number(s)
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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text

06/2023