March 2022

Public assessment summary report

Name of the Finished Pharmaceutical Product:	Lumerax DT 20/120
Manufacturer of Prequalified Product:	Ipca Laboratories Limited Plot no. 255/1, Village Athal Silvassa 396 230 Dadra and Nagar Haveli (U. T.) India
Active Pharmaceutical Ingredient (API):	Artemether and Lumefantrine

1 .Introduction

Based on in depth review of quality, safety and efficacy data, the authority granted a marketing authorization for Lumerax DT 20/120. It is manufactured at Ipca laboratories limited. The active pharmaceutical ingredient of Lumerax DT 20/120 are artemether and lumefantrine. It is drugs used to treat malaria.

Lumerax DT 20/120 is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* in adults, children and infants.

A compressive description of the indications and posology is given in the SmPC.

2 Assessment of quality

Active pharmaceutical Ingredients (APIs)

Arthemeter and lumefantrine are practically insoluble in water but very soluble in dichloromethane. Both APIs are of BCS low solubility across the physiological pH range, hence particle size distribution (PSD) is considered a critical API parameter. PSD forms part of the FPP manufacturer's API specifications, with acceptance criteria set on the information of the API lots used in the FPP biobatch.

Both accelerated and real time stability studies were conducted in three commercial batches. The stability study was found to be acceptable and the following parameters were considered: description, solubility, melting range ,specific optical rotation (1% solution in dehydrated ethanol), loss on drying , related substances (By HPLC) and Assay (By HPLC)

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource dispersible tablets are yellow coloured, circular, flat-faced, bevelled edge and uncoated, with "i" debossed on one side and plain on the other side. The tablets are packed in PVC/PCTFE/PVC-Alu blister cards.

The aim of the development was to formulate a stable dispersible tablet that is pharmaceutically equivalent and bioequivalent to the comparator product Coartem® Dispersible, containing 20 mg artemether and 120 mg lumefantrine.

The choice of excipients was based on the qualitative composition of the comparator product, supported by drug excipient compatibility studies. Optimisation of excipients was performed in order to obtain the desired quality attributes – like dispersion, disintegration and dissolution – matching the comparator product.

Both artemether and lumefantrine possess poor flowability and compressibility hence a wet granulation approach was selected for manufacture of the tablets. The process is typical for tablets and includes sifting, dry mixing, granulation, drying, milling, blending and compression stages.

During the development of the dispersible tablets, the polymorphic forms of artemether and lumefantrine were studied by XRPD to evaluate any change due to processing or ageing. The polymorphic form remained unchanged for both APIs during manufacture and shelf life.

Specifications

The finished product specifications include tests for description, identification of artemether (HPLC, TLC) and lumefantrine (HPLC, UV), average tablet weight, disintegration time (≤ 3 minutes), tablet dimensions, friability, hardness, fineness of dispersion, uniformity of dosage units (by content uniformity), assay (HPLC), dissolution (HPLC detection; 2-point for artemether), related substances (artemether by TLC and lumefantrine by HPLC), moisture content (IR/halogen moisture balance) and microbial limits. The test procedures have been adequately validated.

Other ingredients

Other ingredients used in the tablet formulation includemicrocrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, hypromellose,polysorbate 80, saccharin sodium, crospovidone, flavour cherry permaseal and magnesium stearate. None of the excipients are derived from animal origin.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage condition (24 months data) and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The product proved to be quite stable at both storage conditions in both pack types, showing a slight increase in degradation products though well within agreed limits. Based on the available stability data the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

3. Assessment of Bio-Equivalence

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Lumerax DT 20/120(4 tablets) manufactured by M/s Ipca Laboratories Ltd., India, with Coartem® dispersible (artemether 20 mg + lumefantrine 120 mg dispersible tablets) (4 tablets) of M/s. Novartis Pharma AG, Basle, Switzerland, in normal, healthy, adult, male and female human subjects under non-fasting conditions (study no. ARL/15/709).

The objective of the study was to compare the bioavailability of the stated Lumerax DT 20/120 manufactured for/by Ipca Laboratories Ltd., India (test drug) with the reference formulation Coartem®Dispersible(Novartis Pharma AG) and to assess bioequivalence. The comparison was

performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions.

Test: 4 dispersible tablets Artemether/Lumefantrine 20 mg/120 mg
(artemether 80 mg + lumefantrine 480 mg)
Batch no. FWR40029
Reference: 4 dispersible tablets Coartem®20 mg / 120 mg
(artemether 80 mg + lumefantrine 480 mg)
Batch no. K0042

A 30 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 27 samples within 72 hours post-dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for artemether and lumefantrine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 2 ng/mL for artemether and 100 ng/mL for lumefantrine.

The study was performed with 70 participants; data generated from a total of 66 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence, while 4 subjects withdraw from the study.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artemether and lumefantrine as well as statistical results are summarised in the following tables:

Artemether

Pharmacokinetic Parameter	**Test formulation (T) arithmetic mean ± SD (geometric mean)**	**Reference (R) arithmetic mean ± SD (geometric mean)**	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI (ANOVAlog)**
t_{max} (h)	3.22 ± 0.87	3.09 ± 1.00	-	-
C_{max} (ng/ml)	145 ± 74 (127)	136 ± 60 (124)	102.7	95.5 – 110.5
AUC_{0-t} (ng.h/ml)	452 ± 229 (395)	443 ± 194 (402)	98.3	91.8 – 105.3
AUC_{0-inf} (ng.h/ml)	466 ± 235 (--)	457 ± 201 (--)	--	--

Lumefantrine

Pharmacokinetic Parameter	**Test formulation (T) arithmetic mean ± SD (geometric mean)**	**Reference(R) arithmetic mean ± SD (geometric mean)**	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI (ANOVAlog)**
t_{max} (h)	5.83 ± 0.60	5.84 ± 0.57	-	-
C_{max} (ng/mL)	6678 ± 1998 (6397)	7652 ± 2541 (7260)	88.1	83.1 – 93.5
AUC_{0-72h} (ng.h/mL)	118215 ± 37725 (112477)	137388 ± 45148 (130428)	86.2	81.8 – 90.9

The results of the study show that preset acceptance limits of 80 - 125 % are met by both AUC and C_{max}values regarding artemether and lumefantrine. Accordingly, the test Lumerax DT 20/120 meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to Coartem®Dispersible (Novartis Pharma AG).

4. Conclusion

Based on assessment of data on quality, bioequivalence, safety and efficacy, the assessors considered that the benefit-risk profile of Lumerax DT 20/120 was acceptable for the following indication**:** 'indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* in adults, children and infants'.