This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[HA765 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited
Active Pharmaceutical Ingredient(s) (API)	Dolutegravir (as sodium)
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use, other antivirals (J05AX12)
Therapeutic indication	[HA765 trade name] is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in children at least 4 weeks of age or older and weighing at least 3 kg.

1. Introduction

[HA765 trade name] is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in children at least 4 weeks of age or older and weighing at least 3 kg.

For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines (e.g. those issued by WHO) should be consulted.

[HA765 trade name] should be prescribed by a health care provider experienced in the management of HIV infection.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

Active pharmaceutical Ingredient (API)

Dolutegravir sodium (sodium (4R,12aS)-N-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a hexahydro-2H-pyrido [1',2':4,5] pyrazino[2,1-b] [1,3] oxazine-9-carboxamide) is an off-white to yellow coloured powder. The structure is characterized by FT-IR, UV, 1H-NMR, 13C-NMR, mass spectrometry and elemental analysis. The API is BCS critically insoluble. The API possesses two chiral centers and exhibits isomerism. The manufacturer consistently produces the crystalline anhydrous form and in the micronized grade. The polymorphic form which is obtained by the FPP manufacturer is confirmed by appropriate techniques.

The specifications for dolutegravir sodium include tests for description, solubility, identification (IR, HPLC and sodium), water content (KF), heavy metals, sodium content, related substances (HPLC), enantiomeric purity (HPLC), assay (HPLC), residual solvents (GC), polymorphic identity (pXRD),

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

content of genotoxic impurities (GC; ≤ 15 µg/g), nickel content (ICPMS; ≤ 20ppm), particle size distribution and microbial limits.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packaging.

Other ingredients

Other ingredients used in the core tablet formulation include mannitol, microcrystalline cellulose, sodium starch glycolate, povidone, silicified microcrystalline cellulose, crospovidone, calcium sulphate dihydrate, sucralose and sodium stearyl fumarate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia, and in-house controlled strawberry cream flavour. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/polyethylene glycol and iron oxide red. None of the excipients used in the manufacture of the tablets are of human or animal origin. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink-coloured, capsule-shaped, film-coated tablet debossed with 'K' and '1' and separated by a break-line on one side and another break-line on the other side. The break-line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are presented in a white, round, HDPE bottle with polypropylene child-resistant closure with pulp and white printed heat seal liner. The bottle may or may not contain a 1 g silica gel sachet.

The aim of the development was to formulate a paediatric dispersible oral dosage form, which is stable, and bioequivalent to the WHO comparator product Tivicay® (dolutegravir 5 mg) dispersible tablets. The core tablet is qualitatively similar to the comparator product with respect to composition. The flavouring agent and sweetener were used to improve the taste of the paediatric formulation. Due to the low solubility of dolutegravir sodium, the micronized API was used. The small particle size distribution of micronized API may lead to poor flowability and potential content uniformity issues, therefore wet granulation manufacturing process was developed to ensure homogeneity. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC, UV) and colorants, disintegration time, water content (KF), fineness of dispersion, uniformity of dosage units (by content uniformity), dissolution (UV detection), related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are regarded acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2020 according to internationally accepted guidelines.

Single dose fasting in-vivo bioequivalence study of Dolutegravir sodium dispersible tablet 10 mg (Macleods Pharmaceuticals Ltd., India) with two tablets of Dolutegravir 5 mg dispersible tablets manufactured by GlaxoSmithKline, UK on behalf of ViiV Healthcare, UK in healthy, adult, human male subjects (study BEQ-2602-DOLU-2019).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 10 mg dispersible tablet manufactured by/for Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Tivicay PD 5 mg tablet (GSK) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 dispersible tablet Dolutegravir 10 mg (dolutegravir 10 mg) Batch no. BDF2902A

Treatment R: Reference – 2 tablets Tivicay PD® 5 mg (dolutegravir 10 mg) Batch no. 192416479

The tablets were dispersed in 50 ml water before intake, followed by intake of an additional 50 ml of water. A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for dolutegravir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 15 ng/ml for dolutegravir.

The study was performed with 24 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for dolutegravir as well as statistical results are summarised in the following table:

Dolutegravir

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)	0.86 ± 0.52	0.77 ± 0.39	–	–
C_{max} (ng/mL)	1270 ± 245 (1247)	1291 ± 282 (1263)	98.7	92.8 – 105.1
AUC_{0-t} (ng·h/mL)	20933 ± 4596 (20479)	20502 ± 4101 (20141)	101.7	97.7 – 105.9
AUC_{0-inf} (ng·h/mL)	22293 ± 5727 (21662)	21641 ± 4882 (21170)	102.3	98.3 – 106.6

The results of the study show that preset acceptance limits of 80–125 % are met by both AUC and C_{max} values regarding dolutegravir. Accordingly, the test Dolutegravir 10 mg dispersible tablet meets

the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tivicay PD tablet (GSK).

4. Summary of product safety and efficacy

[HA765 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [HA765 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay PD 5 mg tablet (GlaxoSmithKline) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA765 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [HA765 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA765 trade name] has been shown to be bioequivalent with Tivicay PD 5 mg tablet (GlaxoSmithKline).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA765 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA765 trade name] was acceptable for the following indication: 'in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in children at least 4 weeks of age or older and weighing at least 3 kg', and would allow inclusion of [HA765 trade name], manufactured at Macleods Pharmaceuticals Limited, Block N2, Village Theda, P.O. Lodhimajra, Tehsil Baddi, Dist. Solan, Himachal Pradesh 174101, India, and Macleods Pharmaceuticals Limited, Phase II, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India, in the list of prequalified medicinal products.