This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Dolutegravir 50mg Tablets[1]
Manufacturer of Prequalified Product:	Cipla Limited Indore (Unit –IV) Plot No 9, 10 & 15 Indore Special Economic Zone, Phase II Pithampur, District: Dhar Madhya Pradesh – 454 775 India.
Active Pharmaceutical Ingredient (API):	dolutegravir sodium
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, other antivirals. (J05AX12).
Therapeutic indication:	Dolutegravir (as sodium) 50mg Tablets is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40kg.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Dolutegravir 50mg Tablets is indicated is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40 kg.

Dolutegravir 50mg Tablets should be initiated 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)

The API is the sodium salt of dolutegravir. It is very slightly hygroscopic and contains 2 stereogenic carbon centres. The API is manufactured as a pure enantiomer: sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1', 2':4,5]pyrazino[2, 1-b][1,3]oxazin-7 –olate. Extensive spectral studies, including ^{1}H, ^{13}C and ^{19}F with various techniques, have been provided in support of the structure and absolute configuration of the API.

Dolutegravir sodium is critically insoluble (of BCS low solubility across the physiological pH range), hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications. The API exhibits (pseudo)polymorphism and it has been demonstrated by X-ray powder diffraction (XRPD) and infrared spectroscopy (IR) that the manufacturing process consistently yields one polymorphic form, called Form I. The acceptance criteria for PSD were set on information of the API lot used in the FPP biobatch.

The API specifications include tests for description, solubility, identification of the API (IR, HPLC) and sodium, water content, heavy metals, isomeric purity (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic identity (XRPD), PSD, and rhodium content (ICP-MS). Since the API is critically insoluble, PSD and XRPD also forms part of the retest parameters. The test procedures have been adequately validated.

Other ingredients

Other ingredients used in the core tablet formulation include mannitol, povidone, sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide and sodium stearyl fumarate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, macrogol/PEG, talc, titanium dioxide, iron oxide red and iron oxide yellow. None of the excipients used in the manufacture of the tablets are of animal or human origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a brown coloured, round shaped, biconvex, film coated tablet debossed with "C 50" on one side and plain on the other side. The tablets are presented in HDPE bottles with child resistant caps.

The development of the proposed formulation of the multisource product was based on the pharmacokinetic properties and physico-chemical characteristics of the WHO recommended

comparator product, Tivicay® tablets 50 mg. The selection of the core tablet excipients resulted from information available on the qualitative composition of the comparator product, with colloidal silicon dioxide additionally included as glidant, and supported by API-excipient compatibility studies conducted on binary mixtures.

Due to the sticky nature of the API direct compression as manufacturing process was not considered. Being a low dose formulation (API concentration below 30%), an aqueous wet granulation process would assist to achieve better content uniformity and compressibility as compared to direct compression. Information on the comparator product indicates that wet granulation was also used in its manufacture.

The critically insoluble nature of the API necessitates the incorporation of a surfactant in dissolution medium of the tablets. Based on API solubility data and the recommended method in the USFDA's Dissolution Methods Database, pH 6.8 buffer containing 0.25% sodium lauryl sulfate was selected for the quality control dissolution test. The presence of a surfactant in the medium renders the dissolution test less discriminatory with respect to changes in the solid state properties of the API. Thus control of the polymorphic form and PSD on the API batches used in the manufacture of the tablets is regarded critical.

Specifications

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

Stability testing

Stability studies have been performed 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. The results for all parameters at these storage conditions were within agreed acceptance criteria and no negative trend or atypical results were observed, except for a slight increase in water content. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. **Assessment of Bioequivalence**

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

Study title: An open-label, balanced, randomized, single oral dose, two-treatment, two-sequence, two period, two way crossover bioequivalence study comparing Dolutegravir tablets 50 mg of Cipla Ltd. India with Tivicay® (dolutegravir) 50 mg tablets, of ViiV Healthcare, USA in healthy, adult, human male and/or female study participants under fasting conditions (study no. 27368/15-16).

The objective of the study was to compare the bioavailability of the stated Dolutegravir 50 mg tablets manufactured for/by Cipla Ltd., India (test drug) with the reference formulation Tivicay® (ViiV Healthcare) and to assess bioequivalence. The comparison was performed as a single oral dose, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T: Test – 1 tablet Dolutegravir 50 mg
(dolutegravir 50 mg)
Batch no. ID60527
Treatment R: Reference – 1 tablet Tivicay® Film Coated Tablets, 50 mg
(dolutegravir 50 mg)
Batch no. 4ZP6366

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72 h 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 50 ng/ml for dolutegravir.

The study was performed with 46 participants; data generated from a total of 44 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.45 ± 1.29	2.58 ± 1.36	-	-
C_{max} (ng/ml)	2467 ± 665 (2373)	2790 ± 832 (2664)	89.1	82.7 – 95.9
AUC_{0-t} (ng.h/ml)	50692 ± 16877 (48024)	55152 ± 16858 (52606)	91.3	85.0 – 98.1
AUC_{0-inf} (ng.h/ml)	53704 ± 18795 (50623)	58345 ± 18676 (55448)	91.3	84.9 – 98.1

* geometric mean

Conclusion

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 50mg Tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tivicay® (ViiV Healthcare).

4. Summary of Product Safety and Efficacy

Dolutegravir 50mg Tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and bioavailability Dolutegravir 50mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Tivicay® (ViiV Healthcare) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into account. Reference is made 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 clinical performance of the product 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 Dolutegravir 50mg Tablets is used in accordance with the SmPC.

Bioequivalence

Dolutegravir 50mg Tablets has shown to be bioequivalent with Tivicay® (ViiV Healthcare).

Efficacy and Safety

Regarding clinical efficacy and safety, Dolutegravir 50mg Tablets are considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics is taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of Dolutegravir 50mg Tablets was acceptable for the following indication: **" in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents weighing at least 40kg"** and has advised that quality, efficacy and safety of Dolutegravir 50mg Tablets allow inclusion of Dolutegravir 50mg Tablets, manufactured at Cipla Limited Indore (Unit –IV), Plot No 9, 10 & 15, Indore Special Economic Zone, Phase II, Pithampur, District: Dhar, Madhya Pradesh – 454 775, India, in the list of prequalified medicinal products.