SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets*
Manufacturer of Prequalified Product:	Cadila Pharmaceuticals Limited 1389, Dholka - 387 810 District: Ahmedabad Gujarat State India
Active Pharmaceutical Ingredients (APIs):	Ethambutol, isoniazid
Pharmaco-therapeutic group (ATC Code):	Antimycobacterials (J04AM03)
Therapeutic indication:	Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is indicated for the continuation phase of category I and III tuberculosis with ethambutol and isoniazid as the sole antimycobacterial agents.

* Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is indicated for the continuation phase of category I and III tuberculosis with ethambutol and isoniazid as the sole antimycobacterial agents. Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. Ethambutol is generally contraindicated in patients with optic neuritis. Isoniazid is contraindicated in patients with acute liver disease of any etiology, drug induced hepatic disease, previous isoniazid-associated hepatic injury or severe adverse reactions to isoniazid such as drug fever, chills or arthritis.
It is recommended that therapy is given only on the advice of a physician experienced in the treatment of tuberculosis.

2 Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredients (APIs)

Isoniazid is a class 3/1 API and ethambutol hydrochloride a class 3 API according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*). Consequently the APIs are both regarded as BCS highly soluble.

Both APIs are described in the Ph.Int., Ph.Eur. and the USP and are considered well-established.

The APIs are adequately controlled by their respective quality specifications which are pharmacopoeial based, with additional in-house specifications including bulk density, particle size distribution and residual solvents. The specification for ethambutol hydrochloride includes the class 1 solvent 1,2-dichloroethane, limited at 5 ppm, which is a synthesis starting material.

Other ingredients

Other ingredients used in the core tablet formulation include dicalcium phosphate, gelatin, magnesium stearate, sodium starch glycollate and sorbitol, which are all compendial. The film-coat contains hypromellose, polyethylene glycol, talc, titanium dioxide and Quinoline Yellow aluminium lake. Magnesium stearate and dicalcium phosphate are not of animal origin. Gelatine is obtained from hide cuttings of healthy cattle.

Finished pharmaceutical product (FPP)

Pharmaceutical development
Isoniazid and ethambutol hydrochloride tablets are described in the Ph.Int.

Ethambutol Hydrochloride/Isoniazid 400mg/150mg Tablets are yellow, round, biconvex, film-coated tablet, plain on both the sides. The primary packs are blister cards composed of PVC-PVDC film sealed with aluminium foil. Each blister card contains 10 or 28 tablets.

The manufacturing process consists of wet granulation, drying, screening, lubrication, compression and coating (organic based). Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three consecutive production scale batches demonstrated the consistency of the process and the quality of the product.

The product specifications include description, identification, average weight, uniformity of dosage units, moisture content, disintegration time, dissolution, assay, related substances, residual solvents and microbial limits.

Stability testing
Stability studies have been performed on three production scale batches at 30°C±2°C/70%±5% RH as long-term conditions and for six months at accelerated conditions. The product proved to be chemically and physically stable with no or little negative trends. The stability data supported a shelf-life of 60 months for the FPP when stored not above 30°C in the proposed packaging.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

The following bioequivalence study has been performed in 2005 according to internationally accepted guidelines.

A randomized, open label, single dose, two treatment, two-period, two-sequence, two-way crossover comparative study of two tablets of fix dose combination of Isoniazid 150mg + Ethambutol 400mg (containing isoniazid 150mg + ethambutol 400mg of Cadila Pharmaceuticals Ltd., India) with three tablets of Isozid 100mg (containing isoniazid 100mg) of (Fatol Germany) and two tablets of Myambutol 400mg (containing ethambutol 400mg of Riemser Arzneimittel GmbH & Co) in 24 (+2 stand by) healthy, adult, male, human subjects (study no. 1205/019).

The objective of the study was to compare the bioavailability of the stated isoniazid/ethambutol 150/400 mg fixed dose combination tablet manufactured by Cadila Pharmaceuticals Ltd., India (test drug) with the same dose of the separate reference formulations (Isozid 150 mg tablet, Fatol, and Myambutol 400 mg, Riemser Arzneimittel GmbH) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 2 tablets Isoniazid/ethambutol 150/400 mg (isoniazid +ethambutol 300 +800 mg dose) Batch no. CTA5223.
Treatment R:	Reference – 3 tablets Isozid® 100 mg (isoniazid 300 mg dose) Batch no. 004114. – 2 tablets Myambutol® 400 mg (ethambutol 800 mg dose) Batch no. 303350.

A 7 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 15 samples within 24 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 isoniazid were analyzed using a validated HPLC method with UV detection and drug concentrations for ethambutol were analyzed using validated LC-MS/MS method. The limit of quantification was stated to be about 100 ng/ml for isoniazid and 50 ng/ml for ethambutol.

The study was performed with 26 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 isoniazid and ethambutol as well as statistical results are summarised in the following tables:

Isoniazid

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)	1.44 ± 0.92	1.30 ± 0.55	-	-
C_{max} (µg/ml)	4.70 ± 2.04 (4.32)	4.78 ± 1.30 (4.50)	96.0	84.2 – 109.3
AUC_{0-t} (µg.h/ml)	21.2 ± 9.7 (18.6)	22.3 ± 10.4 (19.4)	95.9	91.3 – 100.6
AUC_{0-inf} (µg.h/ml)	21.7 ± 9.9 (19.7)	22.8 ± 10.7 (20.1)	98.0	93.2 – 103.0

* geometric mean

Ethambutol

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)	3.04 ± 0.86	2.85 ± 1.02	-	-
C_{max} (µg/ml)	2.53 ± 0.95 (2.69)	2.43 ± 0.65 (2.50)	107.7	94.2 – 123.0
AUC_{0-t} (µg.h/ml)	12.2 ± 3.8 (12.2)	11.6 ± 2.7 (12.0)	101.5	95.5 – 107.9
AUC_{0-inf} (µg.h/ml)	13.0 ± 4.1 (13.1)	12.5 ± 2.9 (13.3)	99.6	93.7 – 106.0

* geometric mean

Conclusions:

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding isoniazid and ethambutol. Accordingly, the test fixed dose combination tablet Isoniazid/ethambutol 150/400 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the individual references Isozid® (Fatol) and Myambutol® (Riemser Arzneimittel).

4. Summary of Product Safety and Efficacy

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator products, Isozid® and Myambutol®, 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 as stated in the Summary of Product Characteristics are considered. Reference is made to the SPC (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 Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is used in accordance with the conditions as stated in the SPC.

Bioequivalence

Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets has shown to be bioequivalent with the reference products, Myambutol tablets (Riemser Arzneimittel GmbH & Co) and Isozid tablets (Fatol, Germany).

Efficacy and Safety

Regarding clinical efficacy and safety, Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are considered.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets was acceptable for the following indication: **"for the continuation phase of category I and III tuberculosis with ethambutol and isoniazid as the sole antimycobacterial agents"** and has advised that the quality, efficacy and safety of Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets are acceptable to allow inclusion of Ethambutol hydrochloride/Isoniazid 400mg/150mg tablets, manufactured at Cadila Pharmaceuticals Limited, 1389, Dholka, Ahmedabad, Gujarat State, India in the list of prequalified medicinal products.