

COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ethambutol Dihydrochloride

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ABSTRACT: Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing ethambutol dihydrochloride as the only active pharmaceutical ingredient (API) are reviewed. Ethambutol dihydrochloride is a Biopharmaceutics Classification System (BCS) Class III drug with permeability properties approaching the border between BCS Class I and III. BE problems of ethambutol formulations containing different excipients and different dosage forms have not been reported and hence the risk of bioinequivalence caused by excipients is low. Ethambutol has a narrow therapeutic index related to ocular toxicity. However, as long as the prescribers' information of the test product stipulates the need for regular monitoring of ocular toxicity, the additional patient risk is deemed acceptable. It is concluded that a biowaiver can be recommended for IR solid oral dosage forms provided that the test product (a) contains only excipients present in ethambutol IR solid oral drug products approved in ICH or associated countries, for instance as presented in this paper, (b) complies with the criteria for "very rapidly dissolving" and (c) has a prescribers' information indicating the need for testing the patient's vision prior to initiating ethambutol therapy and regularly during therapy. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 97:1350–1360, 2008

Keywords: absorption; Biopharmaceutics Classification System (BCS); ethambutol; permeability; regulatory science; solubility

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INTRODUCTION

A biowaiver monograph of ethambutol dihydrochloride based on literature data together with some additional experimental data is presented. The risks of basing a bioequivalence (BE) assessment on *in vitro* rather than *in vivo* study results for the approval of new immediate release (IR) solid oral dosage forms containing ethambutol dihydrochloride (“biowaiving”), including both reformulated products and new multisource products, are evaluated under consideration of its biopharmaceutical and clinical properties. This evaluation refers to drug products containing ethambutol dihydrochloride as the only active pharmaceutical ingredient (API) and not its combination products.

The purpose and scope of this series of monographs have been previously discussed.¹ Summarized in few words, the aim is to evaluate all pertinent data available from literature sources for a given API to assess the risks associated with a biowaiver. For these purposes, risk is defined as the probability of an incorrect biowaiver decision as well as the consequences of the decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation can be made as to whether a biowaiver is advisable or not. This systematic approach to recommend or advise against a biowaiver decisions is referred to in the recently published World Health Organization (WHO) Guideline.² Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),³ amitriptyline,⁴ atenolol,¹ chloroquine,⁵ cimetidine,⁶ ibuprofen,⁷ isoniazid,⁸ prednisolone,⁹ prednisone,¹⁰ propranolol,¹ ranitidine,¹¹ and verapamil.¹ They are also available online at <http://www.fip.org/bcs>.

EXPERIMENTAL

Literature data was assessed from PubMed,¹² PubChem,¹³ Medicines Complete,¹⁴ WHO search engine WHOLIS,¹⁵ the BIAM,¹⁶ ROTELISTE,¹⁷ and VIDAL¹⁸ databases. Key words used for searching were: ethambutol, bioequivalence, bioavailability, biowaiver, solubility, permeability, dissolution, tuberculosis, excipient, toxicity, polymorphism, and pharmacokinetics.

GENERAL CHARACTERISTICS

Name

Ethambutol (INN) dihydrochloride;^{19,20}
 ethambutol hydrochloride (INN);^{19,20}
 (+)-(S,S)-2,2'-(ethylenediimino)di-1-butanol dihydrochloride;
 [S-(R*,R*)]-2,2'-(1,2-ethanediyldiimino)bis[1-butanol] dihydrochloride.^{19,20}
 The structure of ethambutol dihydrochloride is shown in Figure 1.

Therapeutic Indications

Ethambutol is one of the key APIs used in the combination treatment of tuberculosis recommended by the WHO.²¹ The standard regime currently calls for an initial therapy for 2 months with isoniazid, rifampicin, pyrazinamide and ethambutol, followed by a continuation phase of 4 months comprising isoniazid and rifampicin. Ethambutol dihydrochloride is added to the combination of the three more powerful antibiotics to prevent the emergence of resistant bacilli.²¹ Ethambutol is also effective against infections caused by mycobacterium avium complex, mycobacterium bovis, and other atypical mycobacteria.²²

Therapeutic Index and Toxicity

WHO,²¹ the Martindale,²² and the British and American Thoracic Society recommend doses of 15 (15–20) mg/kg/day, 15 mg/kg/day, and 15–25 mg/kg/day, respectively. The most serious major adverse drug reaction (ADR) in the treatment with ethambutol dihydrochloride is visual impairment, including irreversible blindness, due to drug-induced optic neuritis.^{23–25} The toxicity is dose related. At doses higher than 30 mg/kg/day the incidence of optic neuropathy increases to 8%. However, this ADR rarely occurs at 15 mg/kg/day.^{17,26} Thus, the margin between the therapeutic doses and doses at which the risk for this ADR increases, is narrow. According to the

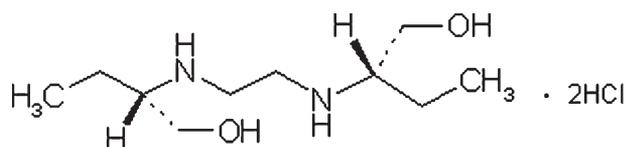


Figure 1. Structure of ethambutol dihydrochloride, M_r 277.23.

current WHO guideline, the onset of this ADR should be managed by immediate interruption of ethambutol treatment.²¹ Toman's Tuberculosis²⁶ recommends that a basic examination should be conducted before starting treatment with ethambutol. Additionally, patients treated with ethambutol should be educated to detect and report changes in vision and be regularly monitored for visual acuity and color vision.^{22,27} Ethambutol should be used with caution in patients with ocular defects (e.g., cataracts, recurrent ocular inflammatory conditions, diabetic retinopathy) and is contraindicated in patients with optic neuritis since in these cases visual changes are difficult to detect or evaluate.^{28,29} For patients with ocular defects the benefits of ethambutol therapy should be carefully weighed against possible ocular adverse effects. Most drug products having a marketing authorization (MA) have a prescribers' information, the Summary of Product Characteristics (SmPCs), containing appropriate cautionary statements as well as instructions for monitoring of vision.

CHEMICAL PROPERTIES

Stereoisomers and Polymorphs

All marketed products employ the therapeutically active stereoisomer (S,S)-ethambutol as the dihydrochloride salt. Therefore, the official national and pharmacopoeial name: ethambutol hydrochloride^{19,20} derived from the INN might be somewhat misleading to those accustomed to standard chemical nomenclature.

Four polymorphic forms have been reported, but only form II is used in drug formulations.³⁰

Solubility

Ethambutol dihydrochloride is readily soluble,³¹ indicating that at least 1000 mg is soluble in 1 mL of water at room temperature.^{19,32,33} Experimental equilibrium solubility data of ethambutol dihydrochloride in compendial standard buffers pH 1.2, 4.5, and 6.8 at 37°C were recently obtained using the standard shake-flask method over 48 h.* The pH of the buffers was monitored and readjusted when necessary to the initial pH

*Experiments performed at the Institute of Pharmaceutical Technology, J.W. Goethe University, Frankfurt am Main, Germany.

values. A validated photometric method previously described in the literature was used for quantification.³³ The literature data and new experimental solubility data are summarized in Table 1.

Partition Coefficient (log *P*)

A log *P* of 0.4 is reported for the system octanol/water, however no detailed information about the test conditions for example, temperature, pH, etc. was provided.³² A computed *X* log *P* of -0.344 is indicated in PubChem.¹³ Kasim et al.³⁴ obtained a log *P* of 0.06 and ClogP[®] of 0.12, respectively, by a calculation method based on atomic contributions to lipophilicity and by the ClogP[®] program.

p*K*_a

Ethambutol is a weak base. At 20°C, p*K*_a values of 6.3²² and 6.6 for the lower p*K*_{a1} and 9.5^{22,31} for the higher p*K*_{a2} were reported. Separately, a p*K*_a value of 6.6³¹ was obtained by a titration technique.

Dosage form Strengths

The WHO Essential Medicines List (EML) lists ethambutol dihydrochloride tablet strengths from 100 to 400 mg.³⁵ Single API dosage forms with a MA in Germany (DE), Finland (FI), France (FR), The Netherlands (NL), and Sweden (SE) contain 100–500 mg. In the United States, MAs exist for strengths in the range from 100 to 400 mg.³⁶

PHARMACOKINETIC PROPERTIES

Permeability and Absorption

No studies investigating *in situ* or *ex vivo* intestinal permeability or Caco-2 cell permeability of ethambutol dihydrochloride were identified. It was reported that ethambutol dihydrochloride is not fully absorbed from the gastro-intestinal (GI) tract and may exhibit unusual pharmacokinetics as a result of transport via the bile duct and/or chelating in the GI tract.³⁷

In an early study, the urinary recovery in patients with tuberculosis was compared to healthy volunteers.³⁸ After 24 h, 45% of the dose

Table 1. Literature Data and New Experimental Data for the Solubility of Ethambutol Dihydrochloride and the Corresponding D/S Ratios for Two Tablet Strengths

Medium	pH	Temperature (°C)	Solubility (mg/mL)	D/S Ratio (mL) ^a	
				400 mg Tablet ^b	500 mg Tablet ^c
New experimental data					
Water		37	649	0.62	0.77
SGF _{sp}	1.2	37	771	0.52	0.65
Phosphate buffer	4.5	37	706	0.57	0.71
SIF _{sp}	6.8	37	747	0.54	0.67
Pharmacopoeial data					
Water		Not defined, about 25°C	≈1000	~0.5	~0.4

^aCut-off limit: ≤250 mL.^{2,59,60}

^bHighest strength on the WHO EML.³⁵

^cHighest strength with a MA in DE, FI, FR, NL, and SE.

was found in the urine of the healthy volunteers, compared to 62% in the patient population. However, these values were based on microbiologic assays and consequently inactive metabolites of ethambutol were not detected.³⁹ Dume et al.⁴⁰ reported a urinary recovery of 46% after oral administration to healthy volunteers. In a later study, Peets et al.⁴¹ administered ¹⁴C radiolabelled ethambutol orally to three patients with advanced, drug-resistant tuberculosis. Urine, feces, and plasma were sampled. In the urine, 54–61% was recovered after 24 h and 67–74% after 144 h. After 48 h, 12–19% of the dose was found in the feces. An additional intravenous (i.v.) dose was also administered to a female patient in this study, enabling the urinary excretion after oral and i.v. dosing to be compared: after i.v. administration, 81% was excreted in the urine within 48 h compared to only 67% after oral intake. Based on these results, the availability of the oral dose is calculated to be 83%. Additionally, only 1% of the i.v. dose was recovered in the feces, compared to 18% after oral administration. It can therefore be assumed that about 20% of an oral dose are not absorbed from the GI tract.⁴¹ Lee et al.^{42,43} reported urinary recoveries of an aqueous solution and a tablet formulation versus i.v. in six healthy volunteers. After 72 h, 79% of the i.v. dose but only 61% (tablet) and 63% (aqueous solution) of the oral doses had been recovered in the urine.⁴³ The absolute BAs were calculated as 77% (tablet) and 80% (solution).³⁷ Kleber et al.⁴⁴ investigated the influence of gastric surgery on the absorption of ethambutol and reported an absolute BA of 89% in partially gastrectomized patients. A microbiological assay

technique, unable to detect nonactive metabolites, was used for quantification.

In an early study, Place et al.^{38,39} determined the dose-dependency of ethambutol absorption, showing that the serum level increased proportionally to the dose over the range of 4–50 mg/kg.

Distribution

Ethambutol is distributed into most body tissues including the lung, kidneys and saliva. It penetrates inflamed meninges (10–50%) to reach therapeutic levels in the CSF.²² Analysis of the erythrocytes indicated accumulation of the API in erythrocytes.³⁹ This finding is consistent with the work of Lee et al.,³⁷ who found a 1.2- to 2.6-fold higher concentration of ethambutol in erythrocytes than in the plasma. In subsequent studies, Place et al.³⁹ and Lee et al.⁴³ observed a concentration ratio of ethambutol in erythrocytes to plasma of 1.1–1.6 and 2, respectively. In an early study, Lee et al.³⁷ determined the plasma protein binding by equilibrium dialysis and ultra filtration against buffer pH 7.4 for 4 h and obtained a value of approximately 20–30%. Plasma protein binding values of 6–30% have also been reported in healthy subjects and in patients with tuberculosis.⁴⁵

Metabolism and Excretion

About 8–15% of the administered ethambutol dose is metabolized in the liver to inactive metabolites, with small interpatient variation; the extent of metabolism is independent of the route of

administration.^{39,41,46} Two metabolites have been identified: an aldehyde intermediate in the oxidation process and a second, more hydrophilic dicarboxylic acid derivate, 2,2'-(ethylenediimino)-di-butyric acid. Chronic administration does not change the metabolic characteristics of ethambutol.³⁸

Elimination half-lives reported for ethambutol range between 1.2 and 4.2 h, depending on the study population, detection method, etc.^{38,40,47} Lee et al.,^{37,43} measured a three to five times higher renal clearance than the creatine clearance after i.v. administration, indicating an active secretion mechanism. Because of the high renal clearance as well as the recovery of a large fraction of the dose intact in the urine, changes in the renal function can alter the kinetics of the antibiotic. These effects were subsequently demonstrated by the same authors in study in a renal insufficient patient.⁴³

Food and Excipient Interactions

Peloquin et al.⁴⁸ investigated the pharmacokinetics of ethambutol dihydrochloride in healthy volunteers under fasted conditions, after a high-fat standard FDA breakfast and after the administration of an aluminum magnesium hydroxide combination antacid. Food did not significantly affect C_{max} and AUC compared to the fasted state, whereas the antacid preparation reduced C_{max} by 29% and AUC by 10%.⁴⁹ These findings are in line with the work of Mattila et al.⁴⁹ and Ameer et al.⁵⁰ who also investigated the influence of food and antacids on the absorption of ethambutol. In separate studies, ethambutol has been shown to form chelates with di- and trivalent cations.⁵¹ The authors subsequently recommended that zinc, copper, or calcium containing preparations, such as antacids or dietary supplements, should be avoided near the time of ethambutol administration.^{27,28}

DOSAGE FORM PERFORMANCE

Bioavailability and Bioequivalence

Lee et al.^{37,43} compared the BA of a single dose oral aqueous ethambutol solution to an unbroken, commercially available tablet formulation in six fasted healthy volunteers. Plasma and urine samples were collected until 72 h post treatment. AUCs, urinary recovery and C_{max} of the tablet and the oral solution tested were not significantly

different.^{42,43} The t_{max} values differed slightly. In a recent *in vivo* study in 20 healthy volunteers, the BE of the products EMB-Fatol[®] 400 and 500 mg, both marketed in DE, were compared to aqueous oral solutions containing the same dose.²⁷ For both strengths, AUC, C_{max} , and t_{max} of the test formulations were not significantly different compared to the oral solutions. No *in vivo* BE studies comparing solid oral ethambutol dihydrochloride formulations from different manufacturers could be identified, but some *in vivo* BE studies comparing fixed dose combinations to formulations containing ethambutol dihydrochloride as the only API in healthy volunteers have been reported. The BE of the products under investigation was confirmed with respect to ethambutol. However, these studies focused on rifampicin and detailed information about the composition of the formulations, etc. was not provided.^{52–55}

Excipients

In vitro, it was demonstrated that ethambutol can form chelates with di- and trivalent metal cations, present in fillers, binders, and lubricants.⁵¹ Table 2 shows the excipients present in ethambutol dihydrochloride IR solid oral drug products with a MA in DE, FI, FR, NL, and SE. It can be inferred that these drug products successfully passed an *in vivo* BE study. In contrast to some other APIs, ethambutol has not been exempted from *in vivo* BE testing in DE.^{56,57} In Table 2 the amounts of the various excipients found in single API ethambutol products, along with the ranges specified by the FDA for oral drug products in general, are given.

Dissolution

The current USP specifies dissolution of $\leq 75\%$ (Q) within 45 min in 900 mL of water in the basket apparatus at a rotation speed of 100 rpm.⁵⁸ Comparative *in vitro* dissolution studies of ethambutol dihydrochloride drug products could not be identified in the literature. The dissolution behavior of an amount of ethambutol dihydrochloride powder equivalent to the highest strength of the WHO EML was experimentally* assessed according to the WHO requirements for BE.² Within 10 min, almost 100% was dissolved in USP SGF_{sp} pH 1.2, in phosphate buffer pH 4.5, and in USP SIF_{sp} pH 6.8.

Table 2. Excipients* Present in Ethambutol Hydrochloride IR Solid Oral Drug Products with a Marketing Authorization (MA) in Germany (DE), Finland (FI), France (FR), The Netherlands (NL), and Sweden (SE), and the Minimal and Maximal Amount of that Excipient Present Pro-Dosage Unit in Solid Oral Drug Products with a MA in the United States

Excipient	Country, Products Containing Named Excipient (See Footnote for Product Names)	Range Present in Solid Oral Dosage Forms with a MA in the USA (mg)
Calcium hydrogen phosphate	DE ^{1,2}	104–850
Castor oil	FI ³	0.03–3.1
Cellulose	DE ^{1,2,4} , FI ³	4.6–1385 ^a
Cellulose acetate phthalate	FI ³	2.4–47.5
Copovidone	DE ^{1,2,4}	86–500
Croscarmellose sodium	DE ^{1,2,4}	2–180
Crospovidone	DE ^{1,2,4}	4.4–792 ^a
Gelatine	DE ^{5,6} , FR ^{7,8} , NL ⁹ , SE ^{10,11}	1–756 ^a
Glycerol	FI ³	0.14–198 ^b
Hypromellose	DE ^{1,2,4–6}	0.8–80
Lactose	DE ^{1,2,4}	23–1020 ^a
Light liquid paraffin	DE ^{5,6} , FR ⁸	0.8–1474 ^a
Liquid paraffin	NL ⁹ , FR ⁷	1.3–50
Macrogol	DE ^{1,2,4} , FI ³ , FR ⁷	0.12–500 ^a
Magnesium stearate	DE ^{1,2,4–6} , FI ³ , FR ^{7,8} , NL ⁹ , SE ^{10,11}	0.9–401 ^a
Povidone	DE ^{1,2,4} , FI ³	0.17–75
Silica	DE ^{1,2,4} , FR ⁷	0.65–99
Sodium lauryl sulphate	DE ^{5,6}	0.65–50
Sorbitan oleate	FI ³	0.11–1.7
Sorbitol	DE ^{5,6} , FR ⁸ , NL ⁹ , SE ^{10,11}	5–337
Starch	FR ⁷	22–616
Stearic acid	DE ^{5,6} , FI ³ , FR ⁸ , NL ⁹ , SE ^{10,11}	0.9–72 ^a
Sucrose	DE ^{5,6} , FR ⁸ , NL ⁹ , SE ^{10,11}	12–900
Talc	SE ¹⁰ , FR ⁷	3–220 ^a

Sources of data: DE: <http://www.rote-liste.de> (assessed 17-08-2006); FI: <http://www.nam.fi> (assessed 18-08-2006); FR: <http://www.vidal.fr> (assessed 23-08-2006); NL: <http://www.cbg-meb.nl> (assessed 17-08-2006); SE: <http://www.lakemedelsverket.se> (assessed 18-08-2006); USA: <http://www.fda.gov/cder/iig/iigfaqWEB.htm#purpose> (version date: July 2006).

*Colorants, flavors and ingredients present only in the coating and/or the printing ink are not included. Drug products containing more than one API were excluded.

^aThe upper range value reported is unusually high for solid oral dosage forms and the authors question its correctness.

^bThe authors have doubts about the correctness of this data. Such amounts are normally present in soft, but not hard gelatine capsules, as indicated by FDA Inactive Ingredients Database.

¹ EMB-Fatol[®] 100 mg Tabletten (Mono).

² EMB-Fatol[®] 400–500 mg Filmtabletten (Mono).

³ Oributol[®] 100–500 mg tabletti.

⁴ EMB-Fatol[®] 250 mg Filmtabletten (Mono).

⁵ EMBHefa 400 Filmtabletten (Mono).

⁶ Myambutol[®] 100–400 mg Filmtabletten (Mono).

⁷ DEXAMBUTOL 500 mg cp pelliculé.

⁸ MYAMBUTOL 400 mg cp pelliculé séc.

⁹ Myambutol, tabletten 400 mg.

¹⁰ Myambutol[®] 100 mg dragerad tablett.

¹¹ Myambutol[®] 400 mg dragerad tablett.

DISCUSSION

Solubility

The solubility values found in the literature were not assessed under conditions specified for the Biopharmaceutics Classification System (BCS)

classification.^{2,59,60} Therefore new solubility determinations were carried out. The time-frame for the solubility determination was extended to 48 h, because the equilibrium solubility was not reached within 24 h. The minimum solubility of ethambutol dihydrochloride was about 700 mg/mL. The corresponding Dose/Solubility (D/S)

ratio, calculated for the highest commercially available tablet strengths on the German market and on the WHO EML, resulted in D/S values of 0.8 mL or lower in the relevant pH range, see Table 1.

An API is “highly soluble” if its D/S ratio is below 250 mL.^{2,59,60} Thus, ethambutol dihydrochloride is “highly soluble.”

Permeability

Values range from 77% to 89% for the extent of absorption of an oral dose of ethambutol, absolute BA and complete urinary recovery. This is consistent with study results which report that about 20% of the oral dose is recovered in the feces (compared to only 1% after i.v. administration) and consequently not absorbed.⁴¹ However, some of these results are not completely reliable because of the assay technique used: radioactive labeling with an incomplete mass balance⁴¹ or microbiological assays⁴⁴ which are not sensitive to inactive metabolites. In summary, it can be concluded that the fraction of dose absorbed of the API is in the range 60–80%.

Given the low molecular weight, the high water solubility and the hydrophilic structure of this API, it can be hypothesized that ethambutol is transported by a paracellular mechanism.

Kasim et al.³⁴ classified ethambutol dihydrochloride as “poorly permeable” based on *in silico* correlations of the partition coefficients $\log P$ and $\text{ClogP}^{\text{®}}$ to intestinal permeability. However, their classification methodology has only limited predictability.⁸ Wu et al.⁶¹ classified ethambutol dihydrochloride in their Biopharmaceutics Drug Disposition Classification System (BDDCS), using elimination and disposition characteristics. Surprisingly, they assigned ethambutol dihydrochloride to BCS Class I, although this API is eliminated renally and mainly unchanged, characteristics that the authors attribute to BCS Class III drugs. Lindenberg et al.⁶² classified ethambutol dihydrochloride as a BCS Class III drug, using literature BA data.

BCS Classification

Ethambutol dihydrochloride is “highly soluble.”^{2,59,60} Data on its oral absorption and permeability are not fully conclusive but suggest this API to be a BCS Class III drug, with permeability properties approaching the border to BCS Class I.

It should be noted that the cut-off for “highly permeable” varies with regulatory authority. The FDA sets a limit for the fraction of dose absorbed of not less than 90%,⁶⁰ the EMEA⁵⁹ requires “high permeability” but does not define a limit for the fraction of dose absorbed and the WHO requires not less than 85% fraction of dose absorbed.²

Up to now, the FDA does not accept biowaivers for BCS Class III APIs, which would exclude ethambutol from biowaiving.^{59,60} On the other hand, the recently revised WHO guidance extended the possibility of a biowaiver approval to BCS Class III APIs under certain conditions.² Therefore ethambutol dihydrochloride is a candidate for biowaiving according to the WHO guidance.

Surrogate Techniques for *In Vivo* Bioequivalence Testing

Ethambutol dihydrochloride is “highly soluble” and the pure drug shows “very rapid dissolution.” Furthermore bioinequivalence of ethambutol dihydrochloride formulations was reported neither *in vivo* nor *in vitro* and is unlikely to occur for this very soluble API. Hence, the stricter dissolution methodology for biowaiving of BCS Class III drugs according the WHO Guidance, that is, “very rapid dissolution” over the pH range of 1.2–6.8, should be capable of detecting poor quality of formulations.² It is noted that the WHO dissolution methodology² uses a 75 rpm rotation speed for the paddle method, whereas the FDA Biowaiver Guideline for the paddle uses 50 rpm.⁶⁰ This increase in rpm was made to reduce the possibility of “coning,” which often occurs at 50 rpm and results in an artefactually slow dissolution rate.

A caveat to the use of dissolution tests as surrogates for *in vivo* BE testing is that *in vitro* dissolution tests are not able to detect excipient influences on permeability and/or GI transit time which may cause bioinequivalence.

Risks of Bioinequivalence Caused by Excipients and/or Manufacturing

Ethambutol was shown to form chelates *in vitro*, but the magnitude of this phenomenon *in vivo* appears to be uncertain in the light of commercial products. For instance, the tablet formulation EMB-Fatol[®], having a MA in DE, contains calcium hydrogen phosphate and no difference in the BA compared to other formulations was

found.²⁷ Furthermore tablet formulations containing ethambutol dihydrochloride as the sole API were found to be bioequivalent to oral solutions *in vivo*. Also, *in vivo* BE studies of ethambutol in fixed dose combinations versus formulations containing ethambutol as the only API, confirmed the BE of the products under investigation. Since no report of a bioinequivalent drug product has appeared in the accessible literature, the risk of bioinequivalence of ethambutol IR dosage forms seems to be low. The risk of bioinequivalence caused by an excipient interaction is further reduced if the test product contains only excipients present in drug products having a MA in an ICH or associated country.⁶³ The excipients present in a number of European countries are listed in Table 2.

Patient Risks Associated with Bioinequivalence

Bioinequivalence of ethambutol IR dosage forms can lead to decreased antituberculosis efficacy on the one hand and to serious, dose-dependent ocular ADRs on the other hand.

In the case of subtherapeutic blood levels, ethambutol dihydrochloride would not fulfill its function in the combination treatment of TB, which is to decrease the emergence of resistance to other components of the multidrug regimen.⁶⁴ However, the risk of bioinequivalence of ethambutol IR dosage forms appears to be relatively low, especially if the test product is formulated only with excipients shown in Table 2 and complies with the criteria for “very rapidly dissolving.”

In case of a supra-bioavailable ethambutol product, serious, dose-dependent ocular ADRs could theoretically occur as a consequence of a higher AUC and/or C_{max} of the test product. However, the therapeutic dose (15–25 mg/kg/day) and the dose at which the risk for this ADR increases, ≤ 30 mg/kg/day, differ by a factor of two. It seems highly unlikely that the test product would show twice the AUC and/or C_{max} of a comparator, with which it has been deemed to be pharmaceutically equivalent, especially when both products have been demonstrated to be “very rapidly dissolving.”² Thus, provided that patients treated with ethambutol containing products are regularly monitored for visual toxicity, the additional risks to the individual patient associated with a biowaiver-based approval can be deemed acceptable. It is noted that most SmPCs for ethambutol products contain such a warning

and have instructions for regular ocular monitoring.

When these conditions are fulfilled by the test product, the additional risk associated with a biowaiver-based approval of solid oral ethambutol dihydrochloride IR formulations appears to be acceptable.

CONCLUSIONS

A biowaiver can be recommended for IR solid oral dosage forms containing ethambutol dihydrochloride provided that the test product (a) contains only excipients present in ethambutol IR solid oral drug products approved in ICH or associated countries, for instance as presented in Table 2, (b) complies with the criteria for “very rapidly dissolving,” and (c) has a SmPC indicating the need for visual testing prior to initiating ethambutol therapy and regularly during therapy, including a description of alarming visual symptoms of acute optic neuritis. When not all these conditions are fulfilled, BE should be established *in vivo*.

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