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Global Health Commentary

Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Amoxicillin Trihydrate

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ABSTRACT

Literature and experimental data relevant to waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate-release solid oral dosage forms containing amoxicillin trihydrate are reviewed. Solubility and permeability characteristics according to the Biopharmaceutics Classification System (BCS), therapeutic uses, therapeutic index, excipient interactions, as well as dissolution and BE and bioavailability studies were taken into consideration. Solubility and permeability studies indicate that amoxicillin doses up to 875 mg belong to BCS class I, whereas 1000 mg belongs to BCS class II and doses of more than 1000 mg belong to BCS class IV. Considering all aspects, the biowaiver procedure can be recommended for solid oral products of amoxicillin trihydrate immediate-release preparations containing amoxicillin as the single active pharmaceutical ingredient at dose strengths of 875 mg or less, provided (a) only the excipients listed in this monograph are used, and only in their usual amounts, (b) the biowaiver study is performed according to the World Health Organization—, U.S. Food and Drug Administration—, or European Medicines Agency—recommended method using the innovator as the comparator, and (c) results comply with criteria for "very rapidly dissolving" or "similarly rapidly dissolving." Products containing other excipients and those containing more than 875 mg amoxicillin per unit should be subjected to an *in vivo* BE study.

Introduction

A monograph on amoxicillin trihydrate based on review of all the available literature studies pertaining to its biopharmaceutical and clinical properties, as well as additional solubility data, is presented. The aim of this monograph is to assess the risks associated with waiving *in vivo* bioequivalence testing of products containing amoxicillin as the sole active pharmaceutical ingredient (API). The possibility of waiving *in vivo* bioequivalence (BE) studies, based on the Biopharmaceutical Classification System (BCS), is described in the Biowaiver Guidance of the U.S. Food and Drug Administration (FDA)[1] and Bioequivalence Guidances of the European Medicines Agency (EMA)[2] and World Health Organization (WHO)[3] for the registration of new or reformulated immediate-release (IR) solid oral dosage forms. In this monograph, the biowaiver decision is discussed not only in terms of the formal requirements set out in the various guidances but also in the context of risks to the individual patient and to public health that would be associated with an incorrect biowaiver decision.

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Methods

Literature studies available in publicly accessible sources (online and printed) on amoxicillin up to May 2016 were identified using the following keywords: amoxicillin trihydrate, biowaiver, BCS, permeability, solubility, and dissolution.

Data were systematically reviewed and are summarized in a layout corresponding to recent biowaiver monographs including those for doxycycline hyclate,[4] ciprofloxacin hydrochloride,[5] isoniazid,[6] and fluconazole.[7]

General Characteristics

Nomenclature

INN name: AmoxicillinTrihydrate [rINN (en)][8]
INN name: Amoxicilinatrihidrato [rINN (es)][9]
INN name: Amoxicilline Trihydrate [rINN (fr)]
INN name: Amoxicillinum Trihydricum [rINN (la)]
Chemical name: (6R)-6-[a-D-(4-Hydroxyphenyl)glycylamino] penicillanic acid.[9]
IUPAC name: (2S,5R,6R)-6-{[(2R)-2-amino-2-(4-hydroxyphenyl)-acetyl]amino}-00-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid.[10]
(2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptanes-2-carboxylic acid trihydrate.[11]

Amoxicillin trihydrate and its salts are included in several pharmacopoeia, for example, the British Pharmacopoeia, in Martindale, The Extra Pharmacopoeia,[9,11] and in the International Pharmacopoeia.[12]

The molecular formula of amoxicillin is $C_{16}H_{19}N_3O_5S$ (anhydrous substance)[11] and its molecular weight is 365.40 g/mol.[9] The molecular weight of amoxicillin trihydrate, $C_{16}H_{19}N_3O_5S.3H_2O$ is 419.4 g/mol.[11] Amoxicillin is available as a white, almost white, or slight pinkish-colored powder or a crystalline solid.[11,13,14] The melting point of amoxicillin is 194 °C,[15] although under a helium atmosphere it is reported to be 190.1 °C.[16] Anhydrous amoxicillin shows a specific optical rotation of +290 to +315.[11] Amoxicillin is also available in pharmaceutical preparations in the salt form, amoxicillin sodium.

The structure of amoxicillin trihydrate is shown in Figure 1.

Therapeutic Uses, Adverse Effects, Toxicity, and Drug Interactions

Amoxicillin is a broad spectrum, beta-lactam antibiotic.[17] It is effective against gram-positive and gram-negative bacteria. Amoxicillin is widely used in the treatment and prevention of susceptible infections including upper and lower respiratory tract infections, gonorrhea, oral infections, otitis media, skin and soft-tissue infections, urogenital tract infections, biliary tract infections, anthrax, endocarditis prophylaxis, and as a part of the treatment of *Helicobacter pylori* infection.[9] Only the parent compound has microbiological activity.[18] Studies of microbiological activity against bacterial strains representing the human colonic flora showed that amoxicillin is active against *Escherichia coli* (MIC_{50} = 5 μg/mL), *Bifidobacterium* (MIC_{50} = 0.06 μg/mL), *Clostridium* (MIC_{50} = 0.1 μg/mL), *Bacteroides* (MIC_{50} = 0.5 μg/mL), *Lactobacillus* (MIC_{50} = 0.25 μg/mL), *Fusobacterium* (MIC_{50} = 0.1 μg/mL), *Eubacterium* (MIC_{50} = 0.1 μg/mL), and *Peptostreptococcus* (MIC_{50} = 0.1 μg/mL).[18]

Amoxicillin has a wide therapeutic index[19] and is well tolerated when given orally. Diarrhea is the most commonly reported adverse effect (incidence of 1 in 10 cases or higher).[13] Nausea, vomiting, irritation of the lower gastrointestinal tract, mucocutaneous candidiasis, and skin rashes are also among the common (incidence of 1 in 10 to 1 in 100 cases) unwanted effects of amoxicillin.[9,13,20] Erythema multiforme and reversible leucopenia are rarely reported adverse effects of amoxicillin.[13]

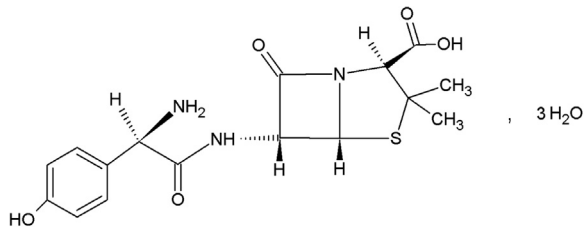

Figure 1. The structure of amoxicillin trihydrate.

Amoxicillin is contraindicated in the presence of penicillin hypersensitivity. The allergens of amoxicillin include both the parent compound and the metabolite.

Animal studies showed no teratogenic effects.[20] In short-term studies of toxicity, the LD_{50} of amoxicillin in nonfasted male rat and mouse was reported as 5000 mg/Kg and in female dogs as greater than 20,000 mg/Kg.[21]

Several interactions with other drugs have been reported for amoxicillin. According to the MHRA assessment report,[20] amoxicillin may reduce the efficacy of oral contraceptives. The assessment report also refers to an interaction with anticoagulants, leading to prolongation of the prothrombin time. Furthermore, it was noted that with concurrent administration of amoxicillin, the absorption of digoxin has been reported to increase. It was also mentioned that the antibacterial activity of amoxicillin may be reduced by coadministration with macrolides, tetracyclines, sulfonamides, or chloramphenicol.[20] Last but not least, the MHRA concluded that the excretion of amoxicillin is delayed in patients with renal impairment.

Amoxicillin is inactivated by bacterial penicillinase.[22-24]

In summary, according to the literature, amoxicillin does not have a narrow therapeutic index and can be safely used with most other drugs, and in most patients, the main exception being those with penicillin allergies.

Dose and Dosage Forms

The usual dose of amoxicillin recommended for an adult is 250 mg every 8 h, which can be doubled in severe infections.[25] For children up to 10 years, 125 mg every 8 h is recommended.

A higher dose of 1 g every 8 h for 3 days is used for otitis media and 1 g twice daily for 2 weeks for *H pylori* eradication. Two doses of 3 g given 8 h apart are recommended for dental infections and urinary tract infections[25] and for prophylaxis of endocarditis before dental or urinary procedures.[25]

Solid oral dosage forms containing amoxicillin trihydrate 250 mg and 500 mg are listed in the 19th list of Essential Medicines (2015) by the WHO.[26] Products of amoxicillin trihydrate listed in pharmacopoeias include capsules (250 mg, 500 mg), tablets (200-1000 mg), chewable tablets (125-500 mg), dispersible tablets (750 mg), oral suspension and dry powder for oral suspension (50-400 mg/mL, 3 g).[11,13,27] However, for the vast majority of clinical indications, solid oral dosage forms containing either 250 mg or 500 mg amoxicillin trihydrate are used. All of the aforementioned doses are based on the milligram amount of amoxicillin trihydrate.

Physicochemical Properties

The United States Pharmacopoeia (USP)[27] and British Pharmacoipoeia[11] have monographs for both amoxicillin trihydrate and amoxicillin sodium.[11] Amoxicillin trihydrate is used in oral dosage forms, whereas amoxicillin sodium is used in parenteral