AMOXICILLIN

DISPERSIBLE TABLETS 250 MG

GENERAL PRODUCT INFORMATION

Amoxicillin is a penicillin-class, effective broad-spectrum antibiotic, which is commonly prescribed to children for treatment of pneumonia and other illnesses, including other bacterial infections of the ears, sinuses, throat, urinary tract, skin, abdomen, and blood. In 2014, WHO published its recommendations for home treatment of pneumonia, establishing amoxicillin as the recommended treatment for pneumonia in children under five.[1] WHO recommends amoxicillin 250 mg dispersible tablets as the most convenient formulation to treat childhood pneumonia in community settings, and especially in remote areas where no reliable sources of clean water and electricity are available. Tablets are cheaper and easier to store and to transport compared with bottled amoxicillin oral suspension. Moreover, minimal manipulation is required prior to the use of a dispersible tablet: it is readily and easily swallowed after adding a small amount of water. This alleviates the need to break or crush adult tablets into smaller pieces before administering a dose to a child or use measuring devices supplied with liquid formulations, which are not accurate and can cause dosing errors.

Amoxicillin 250 mg dispersible tablet is included in the WHO Essential Medicines List and Priority Medicines List for Children.[2] It is also considered an essential medicine for child health by the UN Commission on Life-Saving Commodities for Women and Children.

[1] WHO. *Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities*. Geneva: WHO, 2014. Available at http://www.who.int/maternal_child_adolescent/documents/child-pneumonia-treatment/en/.
[2] WHO. *Priority Medicines for Mothers and Children 2011.* Geneva: WHO, 2011. Available at http://www.who.int/maternal_child_adolescent/documents/emp_mar2011.1/en/.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers approved by UNICEF and those with a proven record of quality products.

2. Procurers should ensure the candidate amoxicillin dispersible tablets have been evaluated by the manufacturer for taste masking. The taste of a dispersible tablet is a crucial parameter that will condition the acceptability by the child and the adherence to treatment. Taste masking is therefore necessary by adding fruit flavors and/or sweeteners to the formulation. The flavors or sweeteners must be common to the areas where the product will be used. Acceptance of the product first by mothers is critical to adherence to treatment by children. A short guide on how to evaluate the taste is described in the Annex.

3. Procurers need to focus on product quality to ensure that it is safe for patient use.

KEY QUALITY CONSIDERATIONS

Product specification

The product must comply with the quality specifications as detailed in the "Product Specifications" section below.

Procurers should ensure products are tested for disintegration time according to the compendial monograph, and the certificate of analysis is checked for disintegration data. Amoxicillin dispersible tablets should completely disintegrate within three minutes when put in a small amount (5–10 mL) of liquid (clean water or milk).

Preference should be given to colorant-free formulations.

Packaging and labeling

Procure tablets only in dispersible form. Amoxicillin dispersible tablets are the most suitable form for treatment of infants and young children. Compared with amoxicillin oral suspension forms, dispersible tablets have advantages in product stability and storage.

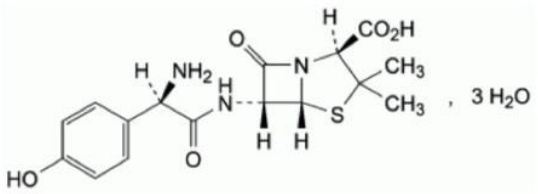
Amoxicillin dispersible tablets that are procured should be packaged in blisters only, as dispersible tablets are water sensitive. Amoxicillin dispersible tablets packaged in bottles or other similar multidose containers will be subjected to humidity each time the container is opened and may start to disintegrate.

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Procurers need to verify with manufacturers that there is satisfactory stability data to support shelf life and storage conditions. The standard shelf life of amoxicillin dispersible tablets is three years when stored at room temperature.

Preference should be given to formulations with long-term stability studies conducted under zone IVa or zone IVb conditions (30°C/65%RH/75%RH).

Name of the Medicinal Product	Amoxicillin 250-mg dispersible tablets
Chemical Name	Amoxicillin trihydrate (2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]-amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate
Chemical Structure	$C_{16}H_{19}N_3O_5S$, $3H_20$ 
Pharmaceutical Form	Dispersible tablets
Qualitative and Quantitative Composition	Each tablet contains amoxicillin trihydrate equivalent to 250 mg amoxicillin. List of typical excipients[3]: – Aspartame – Colloidal anhydrous silica – Magnesium stearate – Microcrystalline cellulose – Crospovidone – Other sweeteners – Flavors
Packaging and Presentation	Amoxicillin dispersible tablets are usually packed in blisters (aluminum/PVC) or strips (aluminum) of 10 tablets.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA and/or recommended by the Expert Review Panel are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

Amoxicillin dispersible tablet 125 mg (scored) and 250 mg (scored) are included in the WHO invitation to manufacturers of medicinal products for treatment of infections in newborn and young infants and childhood pneumonia, to submit an Expression of Interest (EOI) for product evaluation for WHO PQ. As of June 2022, no WHO-prequalified amoxicillin products are available.

[3] Based on the formulation of amoxicillin dispersible tablets approved by EMA and MHRA, although for different strengths.

SRA-approved products

As of June 2022, no SRA-approved amoxicillin 250-mg dispersible tablets are available [4].

When a manufacturer claims that a product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA)
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information—will in all respects be the same as the product approved by the reference SRA

Procurers may cross-check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- UK MHRA: https://products.mhra.gov.uk/
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

UNICEF selects manufacturers among GMP approved manufacturers via tenders (UNICEF contract awards) to supply products usually over a two- or three-year period.[5] The recent lists (from 2020) did not include Amoxicillin 250 mg dispersible tablets.

It is recommended to check for updated information on the UNICEF and WHO PQP websites at the time of procurement.

Related products

Amoxicillin is formulated into conventional capsules ("amoxicillin caps"), tablets ("amoxicillin tabs"), powder for oral suspension ("amoxicillin OS"), and dispersible tablets ("amoxicillin DT"). Many other forms are currently available in the market, including powder for solution for injection or infusion, syrups, sachets, and oral drops.

Amoxicillin caps	–	Amoxicillin capsules are the most widely available pharmaceutical form, available in strengths of 125 mg–1,000 mg.
	–	It is the preferred formulation for adults and can be taken without water if necessary.

[4] Other strengths of amoxicillin dispersible tablets (e.g., 750 mg, 1,000 mg) were found approved and marketed in SRA countries and are indicated for treatment of various bacterial infections.
[5] https://www.unicef.org/supply/contract-awards

Amoxicillin tabs	– Amoxicillin tablets are another conventional form, often available with scoring, available in strengths of 500 mg–1,000 mg. – Scored tablets allow pharmaceutical tablets to be broken and dosing adjusted according to prescription. – They are not as extensively used as capsules and often need to be taken with water.
Amoxicillin OS	– Amoxicillin powder for oral suspension is at present the most commonly used pediatric formulation. – It is administered as a liquid, which facilitates the treatment of children and those with difficulties swallowing solid dosage forms like tablets or capsules. – It is available in the strengths of 125 mg/5 mL to 500 mg/5 mL.

In the WHO Model List of Essential Medicines for Children, the following dosage forms for amoxicillin are listed[6]:

- Powder for oral liquid: 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL
- Solid oral dosage form: 250 mg; 500 mg (as trihydrate)
- Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial

Because the dosage of amoxicillin is based on the child's weight, and because of the potential risks of microbial resistance with underdosing and of toxicity with overdosing, it is crucial that the pediatric formulations have flexibility for dose adjustment. The use of the conventional tablet dosage form often involves breaking a hard adult tablet into smaller pieces, then crushing and adding it to food or liquid; this can lead to inaccuracies in dosing. Liquid dosage forms make weight-based dosing much easier; however, measuring devices supplied with liquid medicines are not accurate and significant under- or overdosing can occur. WHO therefore recommends dispersible tablet dosage forms as the most convenient formulation for children, as they provide greater dosage accuracy, they are less costly than tablets, they have better stability and shelf life than liquids, and they are less bulky to ship and store.

Advantages of amoxicillin dispersible tablets compared to oral suspensions can be described as follows:

- Amoxicillin dispersible tablets are cheaper than its equivalent oral suspensions.
- They offer logistical and supply chain advantages in terms of volume and weight.
- They are also designed to accommodate patients with difficulties in swallowing.
- Amoxicillin dispersible tablets facilitate and simplify community case management (CCM) and provide greater dosage accuracy compared to oral suspensions, which have to be manually measured and mixed.
- Amoxicillin dispersible tablets do not need refrigeration.

STORAGE, STABILITY, AND DEGRADATION

Amoxicillin dispersible tablets have no cold chain storage complications.

Shelf life: 36 months, depending on the manufacturer. It is recommended to check the product label before use.

[6] For use as treatment of community acquired pneumonia (mild to moderate), community-acquired pneumonia (severe), complicated severe acute malnutrition, otitis media, pharyngitis, sepsis in neonates and children, sinusitis, progressive apical dental abscess, and uncomplicated severe acute malnutrition.

Storage condition: Do not store above 30˚C.

Significant breakage of the beta-lactam ring of amoxicillin can occur in hot and humid climatic conditions if inadequate types of packaging are used and storage occurs under inappropriate conditions.

PRODUCT SPECIFICATIONS

The product must meet the USP specifications[7], or the equivalent thereof.

Furthermore, evaluation of taste masking and taste acceptability of the formulation should be conducted during product development to ensure acceptance of the product by children. A short guide on how to evaluate the taste of a medicine has been published by the EMA Committee for Medicinal Products for Human Use, which is summarized in the Annex.

Table A-1. US Pharmacopeia Specifications for Amoxicillin Dispersible Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification (TLC)	The Rf value of the principal spot of the sample solution corresponds to that of the standard solution.	USP<201>
Assay	90.0–110.0%	HPLC, USP<621>
Disintegration	Not more than 3 minutes	USP<701>
Dissolution	Not less than 80% (Q) of the labeled amount of amoxicillin is dissolved.	USP<711>
Uniformity of dosage units	Meet the requirements	USP<905>
Dispersion fineness	A smooth dispersion that passes through a no. 25 sieve is obtained.	As per USP monograph of amoxicillin tablets for oral suspension

[7] As of June 2022, there are no monographs of amoxicillin dispersible tablets published in the International and British Pharmacopeias. Please check updated information at http://apps.who.int/phint/en/p/about/ and in the British Pharmacopeia.

AMOXICILLIN ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

WHO recommends oral amoxicillin as the treatment for childhood fast-breathing and chest-indrawing pneumonia.

Oral amoxicillin is also indicated for the treatment of the following infections in adults and children:

- Acute sinusitis
- Acute malnutrition in infants, children or adolescents (complicated)
- Acute malnutrition in infants, children or adolescents (uncomplicated)
- Bacterial pneumonia (community-acquired pneumonia – mild to moderate)
- Periapical abscess without sinus
- Acute otitis media
- Acute pharyngitis
- Chronic obstructive pulmonary disease with acute exacerbation
- Dental infections
- Sepsis without septic shock (co-prescribed with Gentamicin)
- Bacterial pneumonia (community-acquired pneumonia – severe) in children (co-prescribed with Gentamicin)

Oral amoxicillin is also indicated for the prophylaxis of endocarditis.

Posology, method, and duration of administration

Table A-2. Doses of Amoxicillin for Children 2-59 Months of Age with Pneumonia

CATEGORY OF PNEUMONIA	AGE/WEIGHT OF CHILD	DOSAGE OF AMOXICILLIN DISPERISBLE TABLETS (250 MG)
Fast-breathing pneumonia	2–12 months (4 to < 10 kg)	1 tab twice a day x 5 days (10 tabs)
	12 months–5 years (10–19 kg)	2 tabs twice a day x 5 days (20 tabs)
Fast-breathing and chest-indrawing pneumonia	2–12 months (4 to< 10 kg)	1 tab twice a day x 5 days (10 tabs)
	12 months–3 years (10 to < 14 kg)	2 tabs twice a day x 5 days (20 tabs)
	3–5 years (14–19 kg)	3 tabs twice a day x 5 days 30 tabs)

For other indications

The dose of amoxicillin selected to treat an individual infection should take into account:

- Expected pathogens and their likely susceptibility to antibacterial agents
- Severity and site of infection
- Age, weight, and renal function of the patient; as shown below

The duration of therapy should be determined by the type of infection and response of the patient, and should generally be as short as possible. Some infections require longer periods of treatment.

Children < 40 kg

Children may be treated with capsules, dispersible tablet suspensions, or sachets. Pediatric suspension is recommended for children under 6 months of age. Children weighing 40 kg or more should be prescribed the adult dosage.

Table A-3. Recommended Doses for Children < 40 Kg

INDICATION*	DOSE
Acute bacterial sinusitis, acute otitis media, community-acquired pneumonia, acute cystitis, acute pyelonephritis, and dental abscess with spreading cellulitis	20–90 mg/kg/day in divided doses**
Acute streptococcal tonsillitis and pharyngitis	40–90 mg/kg/day in divided doses**
Typhoid and paratyphoid fever	100 mg/kg/day in three divided doses
Prophylaxis of endocarditis	50 mg/kg orally, single dose 30–60 minutes before procedure
Lyme disease	Early stage: 25–50 mg/kg/day in three divided doses for 10–21 days Late-stage (systemic involvement): 100 mg/kg/day in three divided doses for 10–30 days

** Consideration should be given to the official treatment guidelines for each indication.*
*** Twice-daily dosing regimens should only be considered when the dose is the upper range.*

Adults and children ≥ 40 kg

Table A-4. Recommended Doses for Adults and Children ≥ 40 Kg

INDICATION*	DOSE
Acute bacterial sinusitis, acute pyelonephritis, dental abscess with spreading cellulitis	250–500 mg every 8 hours, 750 mg–1 g every 12 hours For severe infections 750 mg–1 g every 8 hours
Acute otitis media, acute streptococcal tonsillitis and pharyngitis, and acute exacerbations of chronic bronchitis	500 mg every 8 hours, 750 mg–1 g every 12 hours For severe infections 750 mg–1 g every 8 hours for 10 days
Community-acquired pneumonia	500 mg–1 g every 8 hours
Typhoid and paratyphoid fever	500 mg–2 g every 8 hours
Prosthetic joint infections	500 mg–1 g every 8 hours
Prophylaxis of endocarditis	2 g orally, single dose 30–60 minutes before procedure
Lyme disease	Early stage: 500 mg–1 g every 8 hours up to a maximum of 4 g/day in divided doses for 14 days (10–21 days)

INDICATION*	DOSE
	Late-stage (systemic involvement): 500 mg–2 g every 8 hours up to a maximum of 6 g/day in divided doses for 10–30 days

**Consideration should be given to the official treatment guidelines for each indication*

Renal impairment

Table A-5. Recommended Doses for Renal Impairment

GFR (ML/MIN)	CHILDREN < 40 KG*	ADULTS AND CHILDREN ≥ 40 KG
Greater than 30	No adjustment necessary	No adjustment necessary
10–30	15 mg/kg given twice daily (maximum 500 mg twice daily)	Maximum 500 mg twice daily
> 10	15 mg/kg given as a single daily dose (maximum 500 mg)	Maximum 500 mg/day

** In the majority of cases, parenteral therapy is preferred*

Hemodialysis

In patients receiving hemodialysis, amoxicillin may be removed from the circulation by hemodialysis.

Table A-6. Recommended Dose for Adults and Children ≥ 40 Kg

15 MG/KG/DAY GIVEN AS A SINGLE DAILY DOSE.
Prior to hemodialysis, one additional dose of 15 mg/kg should be administered. To restore the circulating drug levels, another dose of 15 mg/kg should be administered after hemodialysis.

In patients receiving peritoneal dialysis: amoxicillin maximum 500 mg/day.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals.

Contraindications

Hypersensitivity to the active substance, to any of the penicillins, or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g., cephalosporin, carbapenem, or monobactam).

Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other beta-lactam agents.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin therapy must be discontinued and appropriate alternative therapy instituted.

Non-susceptible microorganisms

Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible, or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin. This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose, and throat.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses, or in patients with predisposing factors (e.g., history of seizures, treated epilepsy or meningeal disorders).

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment.

Skin reactions

The occurrence at treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP). This reaction requires amoxicillin discontinuation and contraindicates any subsequent administration.

Amoxicillin should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease. It results directly from the bactericidal activity of amoxicillin on the causative bacterium of Lyme disease, the spirochete *Borrelia burgdorferi*. Patients should be reassured this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during, or subsequent to, the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a physician consulted, and an appropriate therapy initiated. Anti-peristaltic medicinal products are contraindicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported.

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Crystalluria

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false-positive readings are common with chemical methods.

When testing for the presence of glucose in urine during amoxicillin treatment, it is recommended that enzymatic glucose oxidase methods be used.

The presence of amoxicillin may distort assay results for estriol in pregnant women.

Important information about excipients

This medicinal product contains aspartame, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria.

Interaction with other medicinal products and other forms of interaction

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate

Penicillins may reduce the excretion of methotrexate, causing a potential increase in toxicity.

Pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Limited data on the use of amoxicillin during pregnancy in humans do not indicate an increased risk of congenital malformations. Amoxicillin may be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Breastfeeding

Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitization. Consequently, diarrhea and fungus infection of the mucous membranes are possible in the breastfed infant, so that breastfeeding might have to be discontinued. Amoxicillin should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of amoxicillin on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g., allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

Undesirable effects

The following categories are used for stating the frequency of undesirable effects: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations

Very rare: mucocutaneous candidiasis.

Blood and lymphatic system disorders

Very rare: reversible leucopenia (including severe neutropenia or agranulocytosis), reversible trombocytopenia, and hemolytic anemia. Prolongation of bleeding time and prothrombin time.

Immune system disorders

Very rare: severe allergic reactions, including angioneurotic edema, anaphylaxis, serum sickness, and hypersensitivity vasculitis.

Not known: Jarisch-Herxheimer reaction.

Nervous system disorders

Very rare: hyperkinesia, dizziness, and convulsions.

Gastrointestinal disorders

Clinical trial data

- * Common: diarrhea and nausea

- * Uncommon: vomiting

Post-marketing data

- Very rare: antibiotic-associated colitis (including pseudomembraneous colitis and hemorrhagic colitis). For oral formulations only, black hairy tongue. For dispersible tablets and oral suspension only, superficial tooth discoloration**.

Hepatobiliary disorders

Very rare: hepatitis and cholestatic jaundice; a moderate rise in AST and/or ALT.

Skin and subcutaneous tissue disorders

Clinical trial data

- * Common: skin rash
- * Uncommon: urticaria and pruritus

Post-marketing data

- * Very rare: skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, and acute generalized exanthematous pustulosis (AGEP)

Renal and urinary tract disorders

Very rare: interstitial nephritis and crystalluria.

Notes

** The incidence of these adverse events was derived from clinical studies involving a total of approximately 6,000 adult and pediatric patients taking amoxicillin.*

*** For dispersible tablets and oral suspension formulations only, superficial tooth discoloration has been reported in children. Good oral hygiene may help prevent tooth discoloration as it can usually be removed by brushing.*

Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms (such as nausea, vomiting, and diarrhea) and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin can be removed from the circulation by hemodialysis.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies who plan to perform a full prequalification of amoxicillin products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on amoxicillin dispersible tablets.

API

Amoxicillin is included in the WHO PQP. As of June 2022, there is no WHO-prequalified amoxicillin API.

Several manufacturers of amoxicillin API have obtained a certificate of suitability for monographs of the European Pharmacopeia (CEP), confirming their quality is suitable for use in medicinal products.

Table A-7. Manufacturers of Amoxicillin API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Amoxicillin trihydrate, powder material, compacted grade A, compacted for direct compression (monograph number 260)	Fersinsa GB S.A. De C.V. MX 25900 Ramos Arizpe, Mexico	R2-CEP 1995-030-Rev 02	6/2/2014	Chemical
Amoxicillin trihydrate, material codes 472191, 472188, 472205, 451787, 440017, 440029, 452360 (monograph number 260)	Sandoz Industrial Products S.A. ES 08520 Les Franqueses Del Vallès, Spain	R2-CEP 1995-034-Rev 06	11/12/2015	Chemical
Amoxicillin trihydrate (monograph number 260)	Aurobindo Pharma Ltd IN 500 038 Hyderabad, India	R1-CEP 2007-147-Rev 03	10/3/2017	Chemical
Amoxicillin trihydrate (monograph number 260)	GlaxoSmithKline Research & Development Ltd, GB TW8 9GS London, UK	R1-CEP 2000-010-Rev 04	6/4/2018	Chemical
Amoxicillin trihydrate, compacted (monograph number 260)	Zhuhai United Laboratories Co, Ltd CN 519 040 Sanzao Town, China	R1-CEP 2007-191-Rev 03	2/6/2019	Chemical
Amoxicillin trihydrate (monograph number 260)	Centrient Pharmaceuticals Netherlands B.V. Delft NL	R1-CEP 2001-367-Rev 05	3/21/2019	Chemical
Amoxicillin trihydrate Enzymatic process (monograph number 260)	Aurobindo Pharma Ltd IN 500 038 Hyderabad, India	R0-CEP 2017-037-Rev 01	16/4/2019	Chemical
Amoxicillin trihydrate (monograph number 260)	Centrient Pharmaceuticals Netherlands B.V. Delft NL	R1-CEP 2007-226-Rev 03	4/24/2019	Chemical
Amoxicillin trihydrate (monograph number 260)	Inner Mongolia Changsheng Pharmaceutical Co., Ltd. Tuoketuo, China	R1-CEP 2007-315 - Rev 02	1/31/2020	Chemical

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Amoxicillin trihydrate (monograph number 260)	Fersinsa GB S.A. De C.V. Ramos Arizpe MX	R0-CEP 2018-178-Rev 01	8/19/2020	Chemical
Amoxicillin trihydrate, micronized, normal and high-density powder (monograph number 260)	Zhuhai United Laboratories Co, Ltd. CN 519 040 Sanzao Town, China	R1-CEP 2006-039-Rev 02	10/16/2020	Chemical
Amoxicillin trihydrate Enzymatic process (monograph number 260)	North China Pharmaceutical Group Semisyntech Co Ltd CN 052 165 Shijiazhuang, China	R1-CEP 2014-220-Rev 00	9/11/2020	Chemical
Amoxicillin trihydrate Enzymatic process (monograph number 260)	GlaxoSmithKline Research and Development Ltd GB UB11 1BT Stockley Park, UK	R1-CEP 2015-064-Rev 00	3/3/2021	Chemistry
Amoxicillin trihydrate (monograph number 260)	Sinopharm Weiqida Pharmaceutical CO., LTD. Datong, China	R0-CEP 2019-244-Rev 01	9/29/2021	Chemistry
Amoxicillin trihydrate Enzymatic process, compacted (monograph number 260)	North China Pharmaceutical Group Semisyntech Co Ltd CN 052 165 Shijiazhuang, China	R1-CEP 2017-009-Rev 00	3/2/2022	Chemistry
Amoxicillin trihydrate (monograph number 260)	Teva Pharmaceutical Industries Ltd Tel Aviv - Jaffa, Israel	R1-CEP 2004-146-Rev 02	3/7/2022	Chemistry
Amoxicillin trihydrate compacted (monograph number 260)	Inner Mongolia Changsheng Pharmaceutical CO., LTD. Tuoketuo, China	R1-CEP 2016-310-Rev 00	3/8/2022	Chemistry
Amoxicillin trihydrate Powder, compacted (monograph number 260)	The United Laboratories (Inner Mongolia) CO., LTD. Bayannaoer, China	R1-CEP 2012-078-Rev 02	4/13/2022	Chemistry
Amoxicillin trihydrate compacted (monograph number 260)	Sinopharm Weiqida Pharmaceutical CO., LTD. Datong, China	R0-CEP 2021-461 - Rev 00	5/18/2022	Chemical

Other manufacturers of amoxicillin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.[1]

Amoxicillin API must meet pharmacopeia specifications such as those of the International Pharmacopeia, European Pharmacopeia, and US Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Preferably, the amoxicillin trihydrate is used as a pelletized form. The equilibrium relative humidity (ERH) of the amoxicillin trihydrate used as API should be carefully controlled by appropriate drying so that it does not adversely affect other aspects of the formulation. Preferably, the ERH is less than 30%, ideally from 10% to 20%.

Due to the sensitivity of this API to temperature and humidity, the U.S. Pharmacopeial Convention (USP) recommends using compacted or directly compressible API for manufacturing of dispersible tablets.[2]

[1] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.
[2] Promoting the Quality of Medicines (PQM). Product Information Report: Amoxicillin. 2017. U.S. Pharmacopeial Convention. Rockville, Maryland.

Excipients

The excipients of amoxicillin dispersible tablets include typical tablet diluent (microcrystalline cellulose), disintegrant (e.g., colloidal anhydrous silica, crospovidone), and lubricant (e.g., magnesium stearate).

Amoxicillin dispersible tablets may contain one or more suitable flavors and sweeteners for greater acceptability. The label should indicate the name(s) and amount(s) of any added substances(s). Such added substances:

- Should be harmless in the amounts used
- Should not exceed the minimum quantity required for providing their intended effect
- Should not impair the bioavailability or the therapeutic efficacy or safety of the preparation
- Should not interfere with the assays and tests used to determine compliance with the pharmacopeial standards

The quality of the raw materials in the formulation can affect the product stability. The insoluble excipients can decrease the dissolution rate of amoxicillin trihydrate. Therefore, the formulation should contain as few excipients as possible, to minimize adverse effects on the product stability.

Manufacturing process

The amoxicillin dispersible tablets should be manufactured using dry granulation or a direct compression method. The U.S. Pharmacopeial Convention (USP) report on Amoxicillin[9] also mentions manufacturing of amoxicillin dispersible tablets using dry granulation followed by tablet compression as a viable route. A wet granulation method is not recommended because the formulation is highly sensitive to moisture and temperature conditions.

Careful monitoring and control of humidity during manufacturing and packaging is required.

Note: The risk for potential presence of elemental impurity in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.

Packaging

Amoxicillin dispersible tablets are usually packed in blisters (aluminum/PVC) or strips (aluminum). Considering that the product needs to be protected from exposure to humidity, the Alu-Alu blister is considered a suitable packaging configuration as it is considered impermeable and highly protective[9].

Suitability of the container should be demonstrated, including the following properties:

Safety

- Declarations of compliance with appropriate food additive regulations (e.g., US FDA or EU regulations).

Protection

- Water vapor permeation (WVTR) and light transmission (LT) rate as per USP<671>

Compatibility

- Accelerated and long-term stability data for the packaged finished products.

Bioequivalence requirements

Amoxicillin is a BCS Class I drug (high solubility, high permeability), which is eligible for a biowaiver provided:

1. The dosage form is rapidly dissolving (as defined below) and the dissolution profile of the multisource (generic) product is similar to that of the comparator product in aqueous buffers at pH 1.2, pH 4.5, and pH 6.8 using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, $f_2 \geq 50$ (or equivalent statistical criterion);
2. If both the comparator and the multisource products are very rapidly dissolving (as defined below) the two products are deemed equivalent and a profile comparison is not necessary.

Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 15 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Rapidly dissolving

A multisource product is considered to be rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 30 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Pharmacopeial buffers (e.g., Ph.Int.) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media. Enzymes (pepsin at pH 1.2 and pancreatin at pH 6.8) may be used if the pharmaceutical product contains gelatin (i.e., capsules or caplets) due to the possibility of cross-linking.

It should be demonstrated that the excipients included in the formulation of the multisource product are well established for use in products containing that API, and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting

absorption (e.g., by effects on gastrointestinal motility or interactions with transport processes) or which might lead to interactions that alter the pharmacokinetics of the API.

It is therefore recommended that the excipients employed be present in either the comparator product or in other products that contain the same API as the multisource product and that have marketing authorizations in ICH-associated countries. Excipients that might affect the bioavailability of the API (e.g., mannitol, sorbitol, or surfactants) should be identified and an assessment of their impact should be provided. These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.

WHO has established the following options as acceptable comparator products:

- Amoxil/Clamoxyl (amoxicillin 125mg/5ml, 250mg/5 ml, and 500mg/5ml powder for oral suspension (bottle), 250 and 500 mg powder for oral suspension in sachet, GlaxoSmithKline Pharmaceuticals)
- Amoxicillin pediatric 50mg/ml powder for oral suspension (Teva Pharmaceuticals Inc., US). The recommended comparator product is approved by US FDA; the comparator product should be obtained from the US.

Notes:

- *The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*
- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.*[3, 4]

EMA guidance on the evaluation of taste masking[5]

Qualitative evaluation of the taste by a taste panel

Consumer testing is acknowledged as providing the best population to assess a product. Consumers are regarded as individuals who are prescreened to be actual users of the product tested, with particular interest as to product quality. In line with this definition and taking into consideration the sensory differences between adults and children, it is evident that the children as a target population are regarded as the most suitable panel for taste assessment of pediatric formulations.

Recommendations for performing taste trials in children

To design a palatability study in children the following parameters need to be considered as key elements:

- The test should be short in order to match children's attention span.

[3] https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[4] https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update
[5] European Medicines Agency. 2005. *Reflection Paper: Formulation of Choice for the Paediatric Formulation.* EMA/CHMP/PEG/194810/2005. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf.

- As children are easily distracted, the test has to be intrinsically motivating and "fun" to do.
- The procedure has to be as easy as possible so that even very young children (e.g., preschoolers) can understand it.
- To ensure reliable assessment preventing confusion by the children and taste fatigue, the number of variants to be tested should be limited to a maximum of four.

Palatability studies are not described in any regulatory guidance but must be considered as clinical studies performed by qualified personnel with ethical committee approval, informed consent from parents or guardians and assent from the child as appropriate. There may be ethical difficulties in designing suitable safe studies in which children can easily participate.

Participation and test performance

Generally, children aged 4 years and older are considered to be able to participate in taste trials. Younger children are very often shy and reluctant. Furthermore, their ability to understand and follow the guidance is sometimes limited; they also may lose interest or have difficulty concentrating during an entire testing period. The failure rate varies up to 50% depending on the design and duration of the test. In addition, they are often unable to communicate their feelings and preferences.

To increase children's understanding and motivation, it is recommended to start with either high concentrations of the testing agent to be assessed (flavor or sweetener) or with known compounds (e.g., commonly used flavors) followed by the more specific, unusual one (e.g., strawberry or cherry followed by passion fruit). In some cases, to begin the test with high concentrations of the testing agent (e.g., sweetener) would be inappropriate due to the unpleasant sweet taste or the bitter aftertaste. Procedures to remove the previous taste may include repeated rinsing of the mouth, eating of salty crackers, and a sufficiently long interval between sessions.

Sensory evaluation: affective and analytical testing, and ranking

Probably the most critical item in sensory evaluation is defining the objective. The test objective will determine the type and age of subjects and the methodology to design, conduct, and interpret the study and its outcome.

- Affective testing includes acceptance/preference testing. Typical questions addressed are "which sample do you prefer," "how much do you like it," and "what don't you like."
- Analytical testing requires the use of objective sensory methodologies aiming to determine the characteristics/properties of the test item, without defining acceptance/preference measures. Analytical testing answers questions such as "which sample is more bitter" or "which sample is different." Analytical methods help define the sensory properties of the medicinal product preparation and differentiate between variants but will not directly predict how much a variant will be liked. It is often used as a technical tool to support development/optimization purposes.
- Ranking is a very straightforward method that can be used for preference or analytical assessment ("please rank samples in order of your personal preference" or "please rank samples in increasing order of bitterness," respectively). The advantage of this method is its simple procedure. However, the study results may be biased due to limited memory and attention of the tester during the entire testing period. This limitation may be more pronounced depending on the age of the subjects participating.

Evaluation principles

In most cases smell, texture, taste, and aftertaste, and sometimes also appearance (e.g., if colored) are addressed. The language used in the questionnaire must be simple, intelligible, and plain for all

participants independent of their age, social skills, and developmental level. It is recommended to utilize commonly used terms relevant to the age of the participants to describe these properties:

- Sweet, salty, sour, and bitter characterizing the taste
- Thin, thick, viscous, gritty aiming to portray the texture of the testing item
- Sweet, salty, sour, and bitter but also astringent, numbness, or freshness for the aftertaste

The following two principles for taste evaluation are established in palatability studies with children: verbal judgment and facial hedonic scale.

- Verbal judgement followed by scoring in a scale of (i.e., 1–5, with a score of 1 corresponding to very good and a score of 5 to very bad) facilitates the statistical evaluation of the data obtained.
- The facial hedonic scale allows the expression of preferences using a pictorial scale.

Children below 5–6 years are not considered able to express differences in taste perception by use of the preferential method. A reliable estimation of differences particularly in this age group (< 5 years) might be achieved using the child's own spontaneous verbal judgements following a control question. The facial hedonic scale cannot be used solely to discriminate between the tastes of tested formulations in the youngest age group. Young children may link the figures with things other than taste (e.g., happy face = I will not stay longer in hospital, sad face = pain or discomfort). Facial expressions and behavior pattern of the subject itself (wry faces, shrugging shoulders, vomiting, or spitting the formulation out) may also reflect the acceptance of the tested formulation. To assure a reliable outcome from a palatability study with young children, it is suggested to involve parents, guardians, or health providers in the study, asking about any discomfort or other observations in relation to the acceptance of the study medicine. Since older children judge more critically than younger ones, they are able to discriminate between the formulations using both the verbal judgment and hedonic scale.

Independent of the age of the children and the evaluation principle selected, it is suggested to include in the questionnaire concluding questions to the overall taste evaluation of the formulation such as "which formulation was the best" or "which formulation tasted worst." Similar approaches may be followed for the assessment of the flavor used: "which of the tested flavors did you like the most" or "which one did you dislike the most.