SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LARGOPEN® 250 mg/5 mL dry powder for suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each 5 mL cup contains;
294.12 mg amoxicillin trihydrate (bovine-derived) equivalent to 250 mg amoxicillin.

Excipients:
Each 5 mL contains;
Sucrose q.s.*

*The amount varies depending on the potency of active substance.

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dry powder for oral suspension
White to off-white, homogeneous powder with raspberry odor

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LARGOPEN is indicated for the treatment of the following infections caused by susceptible bacteria:

- Upper respiratory tract infections; tonsillitis, otitis media, sinusitis, pharyngitis etc. (caused by group A beta-hemolytic *streptococci*, susceptible species of *staphylococci*, *S. pneumoniae*, and susceptible species of *H. influenza*)
- Lower respiratory tract infections; acute and chronic bronchitis, chronic bronchial sepsis, lobar and bronchopneumonia (caused by *Streptococcus* species (α- and β-hemolytic strains only), *S. pneumoniae*, *Staphylococcus* species or *H. influenzae)*
- Urogenital infections; cystitis, urethritis, pyelonephritis, adnexitis, puerperal infections, septic abortus, gonorrhea, prostatitis etc. (caused by *E. coli*, *P. mirabilis* or *E. faecalis*)
- Skin-soft tissue infections; impetigo, cellulitis, abscess, erysipelas, acne (Streptococcus species (alpha and beta hemolytic strains only), *Staphylococcus* species)
- Acute uncomplicated gonorrhea (anogenital and urethral infections) caused by *N. gonorrhoeae* (in men and women).
- Prophylaxis of bacterial endocarditis

- It can also be used in infections such as peritonitis, typhoid, paratyphoid fever, and dental abscess.

It may be preferred to start the treatment with parenteral amoxicillin in some of the abovementioned indications.

In order to reduce the growth of drug-resistant bacteria and to maintain the efficacy of LARGOPEN and other antibacterial agents, LARGOPEN should only be used for the infections caused by bacteria that are proven or strongly suspected to be susceptible.

If culture and susceptibility tests are available, the results of these tests should be used to choose and change antibacterial treatment. When these data are not available, local epidemiological and susceptibility patterns can be based on to choose empirical treatment.

Surgical interventions deemed appropriate should also be implemented when necessary.

4.2. Posology and method of administration
Posology/frequency and duration of administration:
Dosage in adults and children over 3 months of age

Infection	**Severity**	**Dose recommended for adults**	**Dose recommended for children over 3 months of age**
Ear/nose/throat	Mild/moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in two divided equal doses every 12 hours, or 20 mg/kg/day in three divided equal doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in two divided equal doses every 12 hours, or 40 mg/kg/day in three divided equal doses every 8 hours
Lower respiratory tract	Mild/Moderate/Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in two divided equal doses every 12 hours, or 40 mg/kg/day in three divided equal doses every 8 hours
Skin and soft tissue	Mild/moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in two divided equal doses every 12 hours, or 20 mg/kg/day in three divided equal doses every 8 hours
	Severe	875 mg every 12 hours or 500mg every 8 hours	45 mg/kg/day in two divided equal doses every 12 hours, or 40 mg/kg/day in three divided equal doses every 8 hours
Genitourinary system	Mild/moderate	500 mg every 12 hours or 250 mg every 8 hours	25 mg/kg/day in two divided equal doses every 12 hours, or 20 mg/kg/day in three divided equal doses every 8 hours
	Severe	875 mg every 12 hours or 500 mg every 8 hours	45 mg/kg/day in two divided equal doses every 12 hours, or 40 mg/kg/day in three divided equal doses every 8 hours

For the infections caused by less susceptible bacteria, the dosage should be administered as recommended for severe infections.

Frequent bacteriological and clinical evaluation should be performed in chronic urinary tract infections. Doses lower than the recommended dose should not be used. Higher doses may occasionally be necessary. Persistent infections may require continuation of treatment for a few

weeks. Clinical and bacteriological follow-up may also be required to be performed for months after discontinuation of treatment.

Except gonorrhea treatment, treatment should be continued for at least 48-72 hours after the patient is asymptomatic and proof of bacterial eradication is obtained.

For the infections caused by *Streptococcus pyogenes,* it is recommended to continue treatment for at least 10 days in order to prevent acute rheumatic fever.

A single dose of 3 g is administered in gonorrhea caused by *N. gonorrhoeae*, acute uncomplicated anogenital and urethral infections. The necessary tests should be performed in gonorrhea cases with syphilis suspicion, and the patients should be followed for at least 4 months.

Prophylaxis of bacterial endocarditis: For surgical interventions related to gingiva or dental procedures in patients indicated for prophylaxis against bacterial endocarditis, oral amoxicillin is used as 3 g 1 hour before the procedure and 1.5 g 6 hours after the procedure in adults. In children, oral amoxicillin is used as 50 mg/kg 1 hour before the procedure and as 25 mg/kg 6 hours after the procedure.

For parenteral administration, i.m. or i.v. ampicillin 2 g is administered 30 minutes before the procedure, and i.m. or i.v. ampicillin 1 g, or 1.5 g oral amoxicillin is used 6 hours after the procedure. In children, i.m. or i.v. 50 mg/kg is used 30 minutes before the procedure, and i.v. or i.m. ampicillin 25 mg/kg or oral amoxicillin is used 6 hours after the procedure. The pediatric dose should not exceed the dose recommended for adults.

Prophylaxis with another antibiotic should be considered in patients who have used penicillin during the last month. Parenteral amoxicillin administration may be continued with oral therapy depending on the type and severity of the infection.

Route of administration:
The dry powder is reconstituted to prepare LARGOPEN 250 mg suspension for oral administration.
Preparation of suspension:
Add boiled and cooled potable water up to half of the marked line on the bottle and shake well. Wait 5 minutes for a homogeneous distribution. Add water up to the marked line on the bottle and shake again. Each cup of the suspension contains 250 mg amoxicillin.

Additional information on special populations:

Renal/ Hepatic impairment:
Renal impairment:
Dose reduction is not necessary in mild to moderate renal impairment. High doses should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min). Depending on the severity of infection, the dose should be 500 or 250 mg every 12 hours in patients with

creatinine clearance of 10-30 mL/min. Depending on the severity of infection, the dose should be 500 or 250 mg every 24 hours in patients with creatinine clearance less than 10 mL/min.

Depending on the severity of infection, 500 or 250 mg LARGOPEN should be used every 24 hours in patients on hemodialysis. Additional doses may be required during and at the end of the hemodialysis session.

In children with renal impairment weighing less than 40 kg;

Creatinine clearance (mL/min)	Dose	Frequency of administration
10 – 30 mL/min	15 mg/kg	twice a day (maximum 500 mg, 2 times a day)
< 10 mL/min	15 mg/kg	once a day (maximum 500 mg/day)

Hepatic impairment:
There is no specific warning reported for these patients.

Pediatric population:
The dosage recommended for children in the table above is appropriate for those weighing less than 40 kg.
The dose for adults should be used in children with body weight of 40 kg and above.

Since renal function development is incomplete in neonates and small infants, elimination of amoxicillin may be delayed. Dose of amoxicillin should be adjusted carefully in infants younger than 3 months of age. The highest dose of LARGOPEN that may be used in this age group is 30 mg/kg/day and should be given as two equally divided doses every 12 hours.

Geriatric population:
No difference has been observed between the responses of young and elderly patients. However, because elderly patients are more likely to have decreased renal function, the necessity to be more careful should be borne in mind with this patient group. The dose should be chosen carefully and renal functions should be monitored.

4.3. Contraindications

LARGOPEN is contraindicated in patients with hypersensitivity to amoxicillin, penicillin or any of the other ingredients of the product.
Attention should also be paid to possible cross-reactivity with other beta-lactam antibiotics such as cephalosporins.

4.4. Special warnings and precautions for use

Serious and rarely fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving penicillin therapy. These reactions are more common in those with hypersensitivity to several allergens and in parenteral administration compared to oral therapy. Prior to initiation of penicillin therapy, previous hypersensitivity reactions to penicillin, cephalosporin and other allergens should be thoroughly investigated. Serious anaphylactic reactions require immediate treatment with adrenaline. Depending on the indication, oxygen and intravenous steroids should be used, and airways should be maintained open. Intubation should be performed, if necessary.

Cross allergy to penicillins may be reported in patients with hypersensitivity to cephalosporin antibiotics.

Mild or severe pseudomembranous colitis has been reported during treatment with all antimicrobial agents. Diarrhea that occurs during amoxicillin treatment should therefore be considered from this point of view as well. During treatment with antibacterial agents, the normal intestinal flora may be disturbed and this may lead to growth of pathogens from the *Clostridia* group. A toxin produced by *Clostridium difficile* is the most important cause of antibiotic related colitis. While discontinuation of treatment is sufficient in mild cases, severe cases require fluid-electrolyte management and using an antibacterial effective against *C. difficile*.

The possibility of superinfection caused by bacterial pathogens*(Enterobacter, Pseudomonas*) and fungi (*Candida*) should be borne in mind during the treatment. In such cases, treatment should be discontinued and appropriate treatment should be initiated.

Long-term use may cause overgrowth of non-susceptible organisms.

There is an increased risk of erythematous skin rash in patients with infectious mononucleosis. Antibiotics from the amoxicillin groups should therefore not be used in patients with mononucleosis.

As with all other potent agents, it is recommended to monitor renal, hepatic and hematopoietic functions during treatment.

Patients with gonorrhea should be tested for syphilis and the test should be repeated 3 months after termination of LARGOPEN treatment.

Crystalluria has rarely been observed in patients with decreased urination, particularly associated with parenteral therapy. Ensuring adequate urination and sufficient fluid intake is important during administration of amoxicillin at high-doses.

Because amoxicillin is likely to be reduced in patients with renal impairment, it may be necessary to decrease the total daily dose (see Section 4.2).

LARGOPEN contains sugar. Patients with rare hereditary problems such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not use this medicinal product.

4.5. Interaction with other medicinal products and other forms of interaction

Chloramphenicol, macrolides, sulfonamides and tetracyclines, which are bacteriostatic antibiotics, may interfere with the bactericidal activity of penicillins. This interaction has been detected *in vitro*; however, the clinical significance has not been fully explained.

Probenecid decreases the renal tubular excretion of amoxicillin. Concurrent use of amoxicillin and probenecid results in increased and prolonged blood levels of amoxicillin.

As with other antibiotics, LARGOPEN may affect intestinal flora, leading to lowered estrogen absorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

Co-administration with allopurinol increases the risk of allergic skin reactions.

Prolongation of prothrombin time has been reported during concurrent use with anticoagulants. Concurrent use should be appropriately monitored.

Interactions with laboratory tests
Because amoxicillin reaches high concentrations in urine, false positive results may be seen in glucose tests. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions are used.

During use in pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol may occur.

4.6. Pregnancy and lactation

General recommendation
Pregnancy category: B.

Women of child-bearing potential/Birth control (Contraception)
Because it may reduce efficacy of oral contraceptives containing estrogen/progesterone, it is advisable to use another effective contraception method during treatment (see Section 4.5).

Pregnancy
Animal studies have not shown any direct or indirect harmful effects on pregnancy/embryonic/fetal development/delivery and postnatal development.
Caution should be exercised when prescribing to pregnant women.
Studies in mice and rats demonstrated no teratogenic effects, even with doses which are 10 times higher than the dose used in humans. There are no adequate and well-controlled studies in

pregnant women. Because animal reproduction studies are not always predictive of human response, it should be used during pregnancy only if clearly needed.

Oral ampicillin is poorly absorbed during labor. Studies in guinea pigs have shown a mild decrease in uterus tonus and a reduced frequency of contractions with i.v. ampicillin while causing a mild increase regarding the intensity and duration of contractions. It is not known whether amoxicillin causes sudden or delayed undesirable effects during labor, or whether it increases the necessity to use forceps or any other obstetric intervention or resuscitation for the newborn.

Lactation
Penicillins have been shown to be excreted in human milk. Amoxicillin use in nursing mothers may lead to sensitization of infants. Caution should be exercised when it is administered to a breast-feeding woman.
The benefit of breast-feeding for the infant and the benefit of LARGOPEN for the breast-feeding mother should be considered when taking the decision whether to discontinue breast-feeding or, to discontinue LARGOPEN treatment or to avoid treatment.

Reproductive ability/Fertility
Studies in animals demonstrated no adverse effects on fertility. There are no adequate clinical studies in humans.

4.7. Effects on the ability to drive and use machines

No effects have been observed on driving and using machines during treatment with amoxicillin.

4.8. Undesirable effects

Undesirable effects observed in clinical trials and during post-marketing experience are listed according to their frequencies:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (>1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); unknown (cannot be estimated based on the available data).

Infections and infestations
Very rare:
Mucocutaneous candidiasis

Blood and lymphatic system disorders
Very rare:
Hemolytic anemia, reversible thrombocytopenia, reversible leucopenia (severe neutropenia or agranulocytosis) prolonged bleeding time and thrombin time (see Section 4.5)
Unknown:

Anemia, thrombocytopenic purpura, eosinophilia and agranulocytosis have been reported. These reactions are usually reversible upon discontinuation of treatment and are considered to be related with hypersensitivity reactions.

Immune system disorders
Very rare:
Anaphylaxis, angioneurotic edema
Unknown:
Serum sickness–like reactions

Nervous system disorders
Very rare:
Hyperkinesia, dizziness, convulsions. Convulsions may occur in patients with renal impairment or those receiving treatment at high doses.

Gastrointestinal disorders
Common:
Nausea, diarrhea

Uncommon:
Vomiting

Very rare:
Black hairy tongue, and hemorrhagic/pseudomembranous colitis

Hepatobiliary disorders
Very rare:
Although slightly elevated SGOT has been reported its clinical significance is not known.

Unknown:
Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis

Skin and subcutaneous tissue disorders
Common:
Skin rash

Uncommon:
Urticaria and pruritus

Very rare:
Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalized exanthemous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)

Unknown:
Hypersensitivity vasculitis

Renal and urinary disorders
Very rare:
Interstitial nephritis, crystalluria

Other
Very rare:
Tooth discoloration (brown, yellow, or gray staining) has rarely been reported. This can be eliminated with brushing or dental hygiene. Most reports occurred in pediatric patients.

Additional information on special populations:
Patients on triple therapy: no side effect specific for combination treatment with clarithromycin and lansoprazole has been reported during treatment with this combination. The most commonly reported side effects were diarrhea (7%), headache (6%) and taste perversion (5%).

Patients on dual therapy: during combination therapy with amoxicillin and lansoprazole, the most commonly reported side effects in patients receiving dual therapy with amoxicillin 3 times a day plus lansoprazole 3 times a day were diarrhea (8%) and headache (7%).

Reporting suspected adverse reactions
Reporting suspected adverse reactions after approval of the medicinal product is highly important. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals must report any suspected adverse reactions to Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9. Overdose and treatment

Interstitial nephritis and crystalluria leading to oliguric renal impairment has been reported in a limited number of patients. This effect has been reversible upon discontinuation of treatment.

Symptomatic and supportive treatment should be applied in case of overdose. Vomiting may be stimulated or gastric lavage may be performed unless there is any contraindication when overdose is detected in a timely manner. Amoxicillin can be removed with hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactam antibacterials, penicillin group
ATC code: J01CA04

Amoxicillin is a semi-synthetic broad-spectrum penicillin, an ampicillin analog with bactericidal activity against Gram-positive and Gram-negative microorganisms.

Mechanism of action: Similar to ampicillin, it exerts bactericidal effects by inhibiting the synthesis of bacterial cell wall mucopolypeptides during active division process.

It is effective against the following microorganisms:

Aerobic Gram-positive bacteria**:**
Enterococcus feacalis, A group beta-hemolytic *Streptococci*, susceptible *Staphylococci* species and *S. pneumoniae* species, *Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus* (penicillin-susceptible strains only), *Corynebacterium* species, *Bacillus anthracis, Listeria monocytogenes*

Staphylococci resistant to methicillin/oxacillin but susceptible to amoxicillin should be considered as resistant to amoxicillin.

Aerobic Gram-negative bacteria**:**
Escherichia coli (non beta-lactamase secreting strains), *Hemophilus influenzae* (non beta-lactamase secreting strains), *Neisseria gonorrhoeae* (non beta-lactamase secreting strains), *Proteus mirabilis* (non beta-lactamase secreting strains), *Salmonella* species, *Shigella* species, *Bordetella pertussis, Brucella* species, *Neisseria gonorrhoeae, Neisseria meningitidis, Vibrio cholerae, Pasteurella septica*

Helicobacter:
Helicobacter pylori

Anaerobic bacteria:
Clostridium species

5.2. Pharmacokinetic properties

General properties
Absorption:
Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The concentrations in blood range from 3.5 µg/mL to 5 µg/mL and from 5.5 µg/mL to 7.5 µg/mL 1 to 2 hours after oral administration of the doses of 250 mg and 500 mg, respectively. The concentrations in blood range from 1.5 µg/mL to 3 µg/mL and from 3.5 µg/mL to 7.5 µg/mL 1 to 2 hours after oral administration of suspensions of 125 mg/5 ml and 250 mg/5 ml, respectively.

Distribution:
It is readily distributed into most body tissues and fluids. However, it may be distributed into cerebrospinal fluid when meninges are inflamed. Amoxicillin has a low protein binding level of approximately 20%.

Biotransformation:
Amoxicillin is partially metabolized in liver.

Elimination:
Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6-8 hours. Half-life of amoxicillin is 61.3 minutes. Excretion of amoxicillin may be delayed by concurrent administration of probenecid.

Linearity / Non-linearity:
A double dose of amoxicillin leads to an approximately two fold increase in serum levels.

5.3. Preclinical safety data

Long-term studies in animals have not been performed to evaluate carcinogenic potential of amoxicillin. Studies to detect mutagenic potential of amoxicillin alone have not been conducted. Data are available from tests performed with amoxicillin clavulanate. Amoxicillin clavulanate was not mutagenic in the bacterial mutation assay and the yeast gene conversion assay. It was weakly positive in the mouse lymphoma assay. However, the increased mutation frequencies in this assay occurred with decreased cell survival. Amoxicillin clavulanate was negative in the mouse micronucleus test and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in both methods. In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 3-fold of the human dose per mg/m^2).

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Raspberry flavor
Sodium saccharin dihydrate
Carmellose sodium
Erythrosine dye (cochineal)
Disodium EDTA
Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Sucrose (powdered sugar)
Colloidal anhydrous silica

6.2. Incompatibilities

This product has no pharmaceutical incompatibilities.

6.3. Shelf-life

36 months

6.4. Special precautions for storage

Store at room temperature below 30°C.
Once prepared, the suspension can be stored for 7 days at room temperature below 25 °C and for 14 days in the fridge (2 °C to 8 °C).

Close the cap tightly after each use.

6.5. Nature and contents of the container

It is packed in 100 mL graduated, amber Type III glass bottle closed with polyethylene cap, together with 2.5-5 mL graduated cup and package leaflet in a box.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with "Regulation on Control of Medical Waste" and "Regulation on Control of Packaging and Packaging Wastes".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

05286/07382/REN/2020

9. DATE OF AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorization:
Date of renewal: Aug 27, 2020

10. DATE OF REVISION OF THE TEXT