SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

MILOXY-S- SUSPENSION (Amoxicillin Oral Suspension BP 250mg/5ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Label Claim: Each 5ml of the reconstituted suspension contains Amoxicillin Trihydrate BP equivalent to Amoxicillin 250 mg.
Contains Sodium benzoate 23.762mg/5ml as preservative

For excipients see section 6.1

3. PHARMACEUTICAL FORM:

Powder for oral suspension

Light pink coloured powder having pleasant flavor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin is indicated for the treatment of the following infections in adults and children (see section 4.2, 4.4 and 5.1):

- Acute bacterial sinusitis
- Acute otitis media
- Acute streptococcal tonsillitis and pharyngitis
- Acute exacerbations of chronic bronchitis
- Community acquired pneumonia
- Acute cystitis
- Asymptomatic bacteriuria in pregnancy
- Acute pyelonephritis
- Typhoid and paratyphoid fever
- Dental abscess with spreading cellulitis
- Prosthetic joint infections
- Helicobacter pylori eradication
- Lyme disease

Amoxicillin is also indicated for the prophylaxis of endocarditis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Suspension to be administered orally.

Adults: 250 mg -1g four times daily.

Children: 125 mg- 250 mg four times daily.

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals

Method of administration

Amoxicillin is for oral use.

Absorption of Amoxicillin is unimpaired by food.

Therapy can be started parenterally according to the dosing recommendations of the intravenous formulation and continued with an oral preparation.

4.3 Contraindications:

Hypersensitivity to the active substance, to any of the penicillins or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use:

Hypersensitivity reactions

Before initiating therapy with amoxicillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse 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.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain,diarrhoea,

hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

Non-susceptible microorganisms

Amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented andknown to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin(see section 5.1). This particularly applies when considering the treatment of patients with urinary tract infections andsevere 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 (see section 4.8).

Renal impairment

In patients with renal impairment the dose should be adjusted accordingly to the degree of impairment (see section 4.2).

Skin reactions

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom ofacute generalised exanthemous pustulosis (AEGP, see section 4.8). This reaction requires amoxicillin discontinuation andcontra-indicates any subsequent administration.

Amoxicillin should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash hasbeen 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 (see section 4.8). It resultsdirectly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochete*Borreliaburgdorferi*. Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

Prolonged use may also 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 (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea 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 contra-indicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported (see section 4.8).

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring shouldbe undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may benecessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

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 inorder to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.8 and 4.9).

Interference with diagnostic tests

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

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucoseoxidase methods should be used.

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

Important information about excipients

This medicine contains 23.762 mg sodium benzoate in each 5 ml. Sodium benzoate mayincrease jaundice (yellowing of the skin and eyes) in new born babies (up to 4 weeks old)

4.5 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

Normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed acourse of amoxicillin. If co-administration is necessary, the prothrombin time orinternational normalised ratio should be carefully monitored with the addition orwithdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate

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

4.6 Fertility, 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.

Breast-feeding

Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitisation. Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding 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.

4.7 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 (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and skin rash.

The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin, presented by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects

Very common (≥1/10)

common (≥1/100 to <1/10)

uncommon (≥1/1000 to <1/100)

rare (≥1/10,000 to<1/1000)

very rare (<1/10,000)

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 thrombocytopenia and haemolyticanaemia.

	Prolongation of bleeding time and prothrombin time (see section 4.4)
Immune system disorders	
Very Rare:	Severe allergic reactions, including angioneurotic oedemanaphylaxis, serum sickness and hypersensitivity vascu(see section 4.4).
Not known:	Jarisch-Herxheimer reaction (see section 4.4).
Nervous system disorders	
Very Rare:	Hyperkinesia, dizziness and convulsions (see section 4.4).
Not known:	Aseptic meningitis
Cardiac disorders	
Not known:	Kounis syndrome
Gastrointestinal disorders Clinical Trial Data	
***Common:**	Diarrhoea and nausea.
***Uncommon:**	Vomiting.
Post-marketing Data	
Very Rare:	Antibiotic associated colitis (including pseudomembraneous colitis and haemorrhagic colitis see section 4.4). Black hairy tongue Superficial tooth discolouration[#]
Not known	Drug-induced enterocolitis syndrome
Hepato-biliary disorders	
Very Rare:	Hepatitis and cholestatic jaundice. A moderate rise in AST and/or ALT.
Skin and subcutaneous tissue disorders	
***Common:**	Skin rash
***Uncommon:**	Urticaria and pruritus
Post-marketing Data	
Very Rare:	Skin reactions such as erythema multiforme, StevensJohnson syndrome, toxic epidermal necrolysis, bullous and exfoliative dermatitis, acute generalisedexanthematous pustulosis (AGEP) (see

	section 4.4) and drug reaction with eosinophilia and systemic symptoms (DRESS).
Not known	Linear IgA disease
Renal and urinary tract disorders	
Very Rare: Not Known	Interstitial nephritis. Crystalluria (see section 4.4 and 4.9 Overdose)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Signs and symptoms of overdose

Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) and disturbance ofthe fluid and electrolyte balance may be evident. Amoxicillin crystalluria, in some casesleading to renal failure, has been observed. Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.4 and 4.8)

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (seesection 4.4).

Treatment of intoxication

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

Amoxicillin can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Penicillins with extended spectrum;

ATC Code J01CA04

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Pharmacokinetic/pharmacodynamics relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The main mechanisms of resistance to amoxicillin are:

- Inactivation by bacterial beta-lactamases.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints

MIC breakpoints for amoxicillin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 9.0.

Organism	**MIC breakpoint (mg/L)**	
	Susceptible ≤	**Resistant >**
Enterobacterales	8[1]	8
Pseudomonas spp.	-	-
Acinetobacter spp.	-	-
Staphylococcus spp.	Note[2]	Note[2]
Enterococcus spp.[3]	4	8
Streptococcus groups A, B, C and G	Note[4]	Note[4]
Streptococcus pneumoniae	0.5[5]	1[5]
Viridans group streptococci	0.5	2
Haemophilus influenzae,[6,HE]	2	2

Moraxella catarrhalis	-[7]	-[7]
Neisseria gonorrhoeae[8]	Note[8]	Note[8]

Gram-positive anaerobes except *Clostridioides difficile*[9]	4	8
Gram-negative anaerobes[9]	0.5	2
Helicobacter pylori	0.125[10]	0.125[10]
Pasteurella multocida	1	1
Aerococcus sanguinicola and *urinae*	Note[11]	Note[11]
Kingella kingae	0.125[12]	0.125[12]
PK-PD (Non-species related) breakpoints	2	8

[1]Wild type Enterobacterales are categorised as susceptible to aminopenicillins. Some countries prefer to categ wild-type isolates of *E. coli* and *P. mirabilis* as "Susceptible, increased exposure". When this is the case, use th breakpoint S ≤ 0.5 mg/L and the corresponding zone diameter breakpoint S ≥ 50 mm.

[2]Most staphylococci are penicillinase producers, which make them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. When staphylococci test as susceptib benzylpenicillin and cefoxitin they can be reported as susceptible to the above agents. However, the efficacy of formulations, particularly phenoxymethylpenicillin, is uncertain. Isolates that test as resistant to benzylpenicillin susceptible to cefoxitin are susceptible to beta-lactamase inhibitor combinations, the isoxazolylpenicillins (oxac cloxacillin, dicloxacillin and flucloxacillin), nafcillin and many cephalosporins. With the exception of ceftaroline a ceftobiprole, cefoxitin-resistant isolates are resistant to all beta-lactam agents. Ampicillin susceptible *S. sapropare**mecA*-negativeandsusceptibletoampicillin,amoxicillinandpiperacillin(withoutorwithabeta-lactamasei

[3]Susceptibility to ampicillin, amoxicillin and piperacillin with and without beta-lactamase inhibitor can be inferre ampicillin.

[4]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin sus withtheexceptionofphenoxymethylpenicillinandisoxazolylpenicillinsforstreptococcusgroupB.

[5]The oxacillin 1unit disk screen test shall be used to exclude beta-lactam resistance mechanisms. When the sc negative (inhibition zone ≥20 mm) all beta-lactam agents for which clinical breakpoints are available can be rep susceptible without further testing. When the screen is positive (inhibition zone <20 mm) consider susceptible f oxacillin zone ≥8 mm, if oxacillin zone <8 mm see breakpoint recommendations (for oral amoxicillin without an inhibitor).

[6]Beta-lactamase positive isolates can be reported resistant to ampicillin, amoxicillin and piperacillin without inh Tests based on a chromogenic cephalosporin can be used to detect the beta-lactamase.

[7]Most*M.catarrhalis*producebeta-lactamase,althoughbeta-lactamaseproductionisslowandmaygiveweakwith*invitro*tests.Beta-

penicillins and aminopenicillins with inhibitors

[8]Always test for beta-lactamase. If positive, report resistant to benzylpenicillin, ampicillin and amoxicillin. Tests on a chromogenic cephalosporin can be used to detect the beta-lactamase. The susceptibility of beta-lactamas negative isolates to ampicillin can be inferred from benzylpenicillin.

[9]Susceptibility to ampicillin, amoxicillin, piperacillin and ticarcillin can be inferred from susceptibility to benzylpe

[10]The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates f those with reduced susceptibility.

[11]Infer susceptibility form ampicillin susceptibility.

[12]Susceptibility can be inferred from benzylpenicillin susceptibility.

[HE]High exposure for agent

infections. As necessary, expert advice should be sought when the local prevalence ofresistance is such that the utility of the agent in at least some types of infections is questionable

In vitro susceptibility of micro-organisms to Amoxicillin
Commonly Susceptible Species
Gram-positive aerobes:
Enterococcus faecalis Beta-hemolytic streptococci (Groups A, B, C and G) Listeria monocytogenes
Species for which acquired resistance may be a problem
Gram-negative aerobes: Escherichia coli Haemophilus influenzae Helicobacter pylori Proteus mirabilis Salmonella typhi Salmonella paratyphi Pasteurella multocida

Gram-positive aerobes: Coagulase negative staphylococcus Staphylococcus aureus [£] Streptococcus pneumoniae Viridans group streptococcus
Gram-positive anaerobes: Clostridium spp.
Gram-negative anaerobes: Fusobacterium spp.
Other: Borrelia burgdorferi
Inherently resistant organisms [†]
Gram-positive aerobes:
Enterococcus faecium [†]
Gram-negative aerobes: Acinetobacter spp. Enterobacter spp. Klebsiella spp.
Gram-negative anaerobes: Bacteroides spp. (many strains of Bacteroides fragilis are resistant).
Others: Chlamydia spp. Mycoplasma spp. Legionella spp.
[†] Natural intermediate susceptibility in the absence of acquired mechanism of resistance. [£] Almost all S.aureus are resistant to amoxilcillin due to production of penicillinase. In addition, all methicillin-resistant strains are resistant to amoxicillin.

5.2 Pharmacokinetic properties

Absorption:

Absorption Amoxicillin fully dissociates in aqueous solution at physiological pH. It is rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration (Tmax) is approximately one hour.

The pharmacokinetic results for a study, in which an amoxicillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers are presented below.

C_{max}	T_{max} *	AUC $_{(0\text{-}24h)}$	T ½
(µg/ml)	(h)	(µg.h/ml)	(h)
3.3 ± 1.12	1.5 (1.0-2.0)	26.7 ± 4.56	1.36 ± 0.56
*Median (range)			

In the range 250 to 3000 mg the bioavailability is linear in proportion to dose (measured as Cmax and AUC). The absorption is not influenced by simultaneous food intake.

Haemodialysis can be used for elimination of amoxicillin.

Distribution:

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.4 l/kg.

Following intravenous administration, amoxicillin has been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material. Amoxicillin, like most penicillins, can be detected in breast milk (see section 4.6).

Amoxicillin has been shown to cross the placental barrier (see section 4.6).

Biotransformation:

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose.

Elimination:

The major route of elimination for amoxicillin is via the kidney.

Amoxicillin has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/hour in healthy subjects. Approximately 60 to 70% of the amoxicillin is excreted unchanged in urine during the first 6 hours after administration of a standard dose of amoxicillin. Various studies have found the urinary excretion to be 50-85% for amoxicillin over a 24hour period.

Concomitant use of probenecid delays amoxicillin excretion (see section 4.5).

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/ to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.

Renal impairment

The total serum clearance of amoxicillin decreases proportionately with decreasing renal function (see sections 4.2 and 4.4).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies have not been conducted with amoxicillin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Carboxymethyl Cellulose Sodium, Sodium Benzoate, Anhydrous Citric Acid, Purified Talc, Colloidal Anhydrous Silica, Colour Erythrosine Supra, Essence BTM DM 7020A

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36months

6.4 Special precautions for storage

The mixture and diluted mixture should be stored at a temperature not exceeding 25ºC and to be used within 1 week of reconstitution

6.5 Nature and contents of container

100 ml Amber coloured glass bottle with a ring mark packed in printed carton along with pack
insert.

6.6 Instructions for use and handling

Shake well before use. Reconstituted Suspension is stable for seven days only.
Keep all medicines out of reach of children.

7. MARKETING AUTHORISATION HOLDER

Milan Laboratories (India) Pvt. Ltd.
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Road No. 9, Opposite MIDC Office,
Wagle Estate, Thane -400604
India
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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

05903/07425/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29.04.2021

10. DATE OF REVISION OF THE TEXT

July-2023