Unasyn*

Unasyn powder for oral suspension:

Sultamicillin

250 mg/5ml

Unasyn Oral tablets:

Sultamicillin tosylate

375 mg tablets

Reference market:
Germany

AfME markets using this LPD:
Egypt

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

Unasyn 375 mg, tablets

Unasyn 250 mg/5ml, powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Unasyn oral tablets: sultamicillin tosylate
Each tablet contains 506.348 mg sultamicillin tosylate dihydrate equivalent to 375 mg sultamicillin.

Excipient with known effect: Each tablet contains 34.011 mg lactose.

Unasyn powder for oral suspension: sultamicillin
5ml of the prepared suspension contains 250 mg sultamicillin

Excipients with known effect: 5 ml contains 2000 mg sucrose and 75 mg Di-basic Sodium phosphate, anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Powder for oral suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unasyn oral is indicated for infections caused by sultamicillin-susceptible micro-organisms and can be treated with oral penicillin therapy (see section 5.1), such as
- acute bacterial sinusitis,
- acute bacterial otitis media,
- tonsillitis,
- community acquired pneumonia,
- acute exacerbation of chronic bronchitis,
- renal infections and infections of the efferent urinary tract,
- skin and soft tissue infections.

Furthermore, Unasyn oral is indicated for the treatment of uncomplicated gonorrhea.
Sultamicillin may also be indicated in patients requiring sultamicillin therapy following initial treatment with sulbactam/ampicillin IM/IV.

The official guidelines for the appropriate use of antibacterial active substances must be considered when using Unasyn oral.

4.2 Posology and method of administration

Posology
The recommended dose in adults and children weighing more than 30 kg is 375-750 mg sultamicillin (1-2 tablets or 7.5-15 ml prepared suspension) twice daily.

Infants and children weighing up to 30 kg usually receive a sultamicillin dose of 50 mg/kg body weight per day divided in 2 individual doses. For this purpose, the use of Unasyn oral powder for oral suspension (for preparation of suspension) is preferably recommended.

Dosage examples for Paediatric population:

Age (weight)	Sultamicillin daily dose equivalent to 50 mg/kg body weight
1 to 3 years (approx. 10-15 kg) 3 to 5 years (approx. 15-20 kg) 5 to 7 years (approx. 20-25 kg) 7 to 9 years (approx. 25-30 kg)	Twice 5.0 to 7.5 ml (Twice 1 to 1 ½ measuring spoon) Twice 7.5 to 10.0 ml (Twice 1 ½ to 2 measuring spoons) Twice 10.0 to 12.5 ml (Twice 2 to 2 ½ measuring spoons) Twice 12.5 to 15.0 ml (Twice 2 ½ to 3 measuring spoons)

The principal route of excretion of sulbactam and ampicillin following oral administration of sultamicillin is via the kidneys. Because renal function is not yet fully developed in neonates, this should be considered when using sultamicillin in neonates.

In the treatment of uncomplicated gonorrhea, Unasyn oral can be given as a single oral dose of 2.25 g (= 6 tablets). In addition, 1 g of probenecid should be taken to achieve sustained serum levels of the active substances.

In patients with severe impairment of renal function, (creatinine clearance ≤ 30 ml/min), the elimination kinetics of sulbactam and ampicillin are similarly affected and hence the plasma ratio of one to the other will remain constant. The dosage intervals of sultamicillin in such patients should be increased in accordance with the usual practice for ampicillin.

Dosage recommendation for patients with impaired renal function:

Creatinine clearance	Dosage interval
5-14 ml/min	24 hours
<5 ml/min	48 hours

Method of administration

Unasyn oral can be taken with or between meals.

The duration of treatment depends on the course of disease. Depending on the severity of infection it should generally be 5 to 14 days. In severe cases, treatment can be continued for a longer period. Treatment should be continued up to 48 hours after subsidence of fever and other symptoms.

It is recommended that there be at least 10 days treatment for any infection caused by ß-hemolytic streptococci to prevent late complications (rheumatic fever, glomerular nephritis).

Unasyn oral tablets
The tablets should be taken if possible in the upright position with fluid to avoid possible lesions of the oesophagus if the retention time in the oesophagus is too long.

Unasyn powder for oral suspension (for instructions on reconstitution of the medicinal product before administration see section 6.6)

Shake before each use!

The package of Unasyn powder for oral suspension (for preparation of a suspension) contains a measuring spoon allowing the administration of 2.5 ml (corresponding to 1/2 of a measuring spoon), 5 ml (corresponding to 1 measuring spoon) or 7.5 ml (corresponding to 1 ½ measuring spoon).

4.3 Contraindications

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

Because of the risk of an anaphylactic shock, use of Unasyn oral is contraindicated in individuals with a history of an allergic reaction to any of the penicillins. Before initiating therapy with Unasyn oral, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins and other allergens as such reactions are more apt to occur in these individuals when receiving Unasyn oral therapy. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted.

In patients with mononucleosis or lymphatic leukemia simultaneous bacterial infections should not be treated with Unasyn oral as such patients tend more frequently to develop morbilliform skin reactions.

Unasyn oral is not indicated in patients with severe gastrointestinal disorders with vomiting and diarrhea as sufficient absorption is not guaranteed.

Unasyn oral should not be used in infants with recurrent diarrhea, with the exception of a short-term continuation of parenteral treatment with Unasyn.

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy including sultamicillin. These reactions are more apt to occur in individuals with a history of penicillin, cephalosporine hypersensitivity and/or hypersensitivity reactions to multiple allergens. Severe acute hyper-sensitivity reactions may manifest themselves as: angioedema, swelling of the tongue, inner swelling of the larynx with

constriction of the airways, severe skin reactions, palpitations, dyspnoea, drug fever, serum sickness, and nephritis, drop in blood pressure, anaphylactoid reaction, anaphylactic shock.

If allergic reactions occur, the drug must be discontinued and an appropriate therapy should be initiated.

Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen and/or intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), exfoliative dermatitis and erythema multiforme have been reported in patients who received oral administration of Unasyn. If patients develop a severe skin reaction, treatment with oral Unasyn should be discontinued and appropriate therapeutic measures introduced (see section 4.8 Undesirable effects).

An immediate reaction of the skin in the form of urticarial exanthem suggests in most cases a genuine penicillin allergy and necessitates discontinuation of therapy.

An antigen community may exist between skin fungi and penicillin so that, in persons suffering from fungal infection of the skin or who had suffered from such an infection, hypersensitivity reactions like after second contact cannot be excluded, even after the first administration of penicillin.

For precautionary reasons, during therapy for more than one week, hepatic enzyme values and the carbohydrate metabolism should be monitored, although the use of Unasyn oral in diabetics did not reveal any clinically relevant effects on glucose availability.

Periodic monitoring of blood count as well as renal and hepatic function should be carried out during prolonged therapy (more than 14 days).

Treatment with Unasyn oral may influence the following laboratory parameters: non-enzymatic methods for the determination of urinary sugar may have a positive result. Urobilinogen tests may be disordered.

After administration of ampicillin to pregnant women, a transient decrease in the plasma concentration of different estrogens was observed. This effect could also occur under therapy with Unasyn oral.

As with any antibiotic therapy, constant observation for signs of overgrowth of non-susceptible organisms, including fungi, is essential. Should superinfection occur, the drug should be discontinued, and/or appropriate therapy instituted.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Unasyn oral, and may range in severity from mild diarrhea to severe and persistent diarrhea. In these cases, antibiotic-induced pseudomembraneous colitis, which may rarely occur and may be life-threatening or fatal, must be considered. Treatment with antibiotics alters the normal flora of the colon leading to overgrowth of *C. difficile.* Therefore, Unasyn Oral should be immediately discontinued in these cases and appropriate therapy initiated (e.g. oral vancomycin, four times 250 mg daily). Hypoperistaltic drugs are contra-indicated.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Medicinal product-induced liver damage including cholestatic hepatitis with jaundice have been associated with the use of Unasyn oral. Patients should be advised to contact their doctor if they experience signs and symptoms of emerging liver disease (see section 4.8 Undesirable effects).

Seizures may occur, as with all penicillins, due to very high serum levels. Therefore dosing should be carried out with caution, in particular in patients with impaired renal function.

The typical morbilliform ampicillin exanthem occurring 5 to 11 days after starting treatment allows further treatment with penicillin derivatives.

Unasyn oral tablets contain lactose
Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Unasyn oral tablets.

Unasyn powder for oral suspension contains sucrose and sodium
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take Unasyn oral powder for oral suspension.
5 ml (corresponding to 1 measuring spoon of the prepared suspension) contain 2 g sucrose (sugar) equivalent to approx. 0.17 dietetic units. This is to be observed in patients with diabetes mellitus.
5 ml (equivalent to 1 measuring spoon) of the prepared suspension contain 13.47 mg sodium. This is to be observed in persons with a restricted sodium (low sodium/salt) diet.

4.5 Interaction with other medicinal products and other forms of interaction

The following drug interactions between the present drug and other drugs are of importance:

Other antibiotics or chemotherapeutical agents
Unasyn oral should not be combined with other bacteriostatic chemotherapeutical agents or antibiotics such as tetracyclines, erythromycin, sulfonamides or chloramphenicol as a decrease in efficacy is possible.

Allopurinol
Gout patients receiving allopurinol have an increased risk of skin reactions if Unasyn oral is co-administered.

Anticoagulants
Penicillins can produce alterations in platelet aggregation and prothrombin time. These effects may be additive with anticoagulants.

Methotrexate
Concurrent use of methotrexate and penicillins has resulted in decreased clearance of methotrexate and a corresponding increase in methotrexate toxicity. Patients should be closely monitored. Leucovorin dosages may need to be increased and administered for longer periods of time.

Probenecid
As a result of inhibited renal excretion (tubular secretion), co-administration of probenecid leads to higher and prolonged ampicillin and sulbactam levels in the serum and ampicillin concentrations in the bile, prolonged elimination half-life, and increased risk of adverse reactions.

Hormonal contraceptives
In rare cases, therapy with aminopenicillins such as ampicillin may question the reliability of the contraceptive efficacy of hormonal contraceptives. Therefore, it is recommended to use non-hormonal contraceptive methods in addition.

Non-steroidal anti-inflammatory drugs
Acetylsalicylic acid, indomethacin and phenylbutazone may prolong the elimination of penicillins.

4.6 Fertility, pregnancy and lactation

Use during pregnancy
Ampicillin and sulbactam cross the placental barrier. Insufficient experience so far with the use of ampicillin/sulbactam in pregnant women has revealed no evidence of harm to the foetus. There is, however, no experience with the use of ampicillin/sulbactam during the 1st trimester of pregnancy. Animal studies with ampicillin and sulbactam have revealed no effects with regard to reproduction toxicity.
As a precaution, this medicinal product should only be used during pregnancy if, in the judgement of the physician, the potential benefits outweigh the potential risks.

Use during breastfeeding
Ampicillin passes into breast milk. Diarrhea and yeast colonisation of the mucous membranes may occur in the breast-fed infant. Possible sensitization should be considered. If treatment of the mother with Unasyn Oral is considered absolutely necessary, the patient should discontinue breast-feeding during treatment as a precaution.

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. It should be considered that dizziness may occasionally occur.

4.8 Undesirable effects

The most common side effects of Unasynoral affect the gastrointestinal system and are usually mild to moderate. Cessation of therapy due to side effects is only rarely necessary.

Treatment with Unasynoral should be discontinued if severe hypersensitivity reactions (angioedema, tongue swelling, inner swelling of the larynx with constriction of the airways, palpitations, dyspnea, drug fever [usually occurs between 7 and 10 days after initiation of therapy], serum sickness [symptoms occur within 14 days], nephritis, drop in blood pressure , anaphylactoid reaction to anaphylactic shock), severe skin reaction, severe and persistent diarrhea and antibiotic-related pseudomembranous colitis, which is rare and life-threatening, occured. Appropriate treatment should be initiated (see section 4.4 Special warnings and precautions for use).

Organ System Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**	**Not known (cannot be estimated from the available data)**
Infections and infestations		Candida infection				Pathogen resistance
Blood and lymphatic system disorders			Thrombo-cytopenia		Bone marrow failure	*Agranulocytosis** *Haemolytic anaemia** *Thrombocytopenic purpura** Pancytopenia Leukopenia *Neutropenia** *Eosinophilia** *Anaemia** Bleeding time prolonged° Prothrombin time prolonged°
Immune system disorders						Anaphylactic shock *Anaphylactoid shock** Anaphylactoid reaction Hypersensitivity Laryngeal oedema

						Angioedema. Swollen tongue Drug fever Serum sickness
Metabolism and nutrition disorders						Anorexia
Nervous system disorders		Headache	Dizziness	*Seizure**		Neurotoxicity
Cardiac disorders						Palpitations
Vascular disorders						Allergic vasculitis
Respiratory, thoracic and mediastinal disorders						Dyspnoea
Gastro-intestinal disorders	Diarrhoea Loose stools	Vomiting Abdominal pain Nausea	Melaena *Glossitis**	Enterocolitis Pseudomembranous colitis		Enterocolitis haemorrhagic Abdominal pain upper Black hairy tongue (tongue discolouration) Flatulence Dysgeusia Stomatitis* Dry mouth
Hepatobiliary disorders			*Hyperbilirubinaemia**			*Cholestatic hepatitis** *Cholestasis** *Hepatic cholestasis** Hepatic function abnormal Jaundice Aspartate aminotransferase increased Alanine aminotransferase increased (see section 4.4)

Skin and sub-cutaneous tissue disorders		Rash (exanthema) Pruritus	Dermatitis Urticaria Skin reaction	Stevens-Johnson-syndrome Toxic epidermal necrolysis Erythema multiforme *Dermatitis exfoliative* *		*Acute generalised exanthematous pustulosis (AGEP)** Urticarial exanthema Rash maculo-papular Rash morbilliform (see section 4.4)
Musculo-skeletal and connective tissue disorders			Arthralgia			
Renal and urinary disorders				*Tubulointerstitial nephritis**		Nephritis
General disorders and administration site conditions			Fatigue Somnolence Malaise			Mucosal inflammation
Investigations						*Platelet aggregation abnormal** Drop in blood pressure

* The adverse reactions in *italics* were observed with the use of ampicillin and/or sulbactam/ampicillin via the IM/IV route.

° These signs are reversible.

It is to be expected that adverse reactions observed with ampicillin therapy may also occur under therapy with Unasyn oral.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local requirements.

To report any side effect(s):

Pharmacovigilance center, Pfizer Pharmaceutical Company: EGY.AEReporting@pfizer.com

Egyptian Pharmacovigilance center (EPVC), CAPA: PV.Center@Eda.mohealth.gov.eg

4.9 Overdose

Limited information is available on the acute toxicity of ampicillin/sulbactam in humans. Overdosage of the drug would be expected to produce manifestations corresponding to the side effect profile of Unasyn oral (see section 4.8). In case of overdose, the adverse drug reactions reported are expected to occur more frequently and in a more severe extent. Very high doses of beta-lactam antibiotics may lead to cerebral (epileptic) seizures. As ampicillin and sulbactam are both removed from the circulation by hemodialysis, hemodialysis may enhance elimination of the drug from the body in the event of overdosage in patients with impaired renal function.

Anaphylactic shock, which is no genuine poisoning, occurs very rarely, but is always acutely life-threatening.

Treatment
Sedation with diazepam for the treatment of cramps due to overdosage. In cases of anaphylactic shock, immediate initiation of appropriate therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Sultamicillin is an orally administerable ester from ampicillin and the beta-lactamase inhibitor sulbactam, which is rapidly broken up in the body into its two components.

Ampicillin is a semi-synthetic, non-beta-lactamase resistant aminopenicillin.
Sulbactam is a beta-lactamase inhibitor structurally related to that of ampicillin and other penicillins.

ATC code

J01CR04

Mechanism of action

The mechanism of action of ampicillin is based on an inhibition of the bacterial cell wall synthesis (in the growth phase) via blocking the penicillin-binding proteins (PBPs) like, for example, the transpeptidases. This results in a bactericidal effect.
In combination with sulbactam, the inactivation of ampicillin caused by certain beta-lactamases is inhibited. Sulbactam protects ampicillin against the breakdown by most beta-lactamases of staphylococci as well as some plasmid-coded beta-lactamases (e.g. TEM, OXA, SHV, CTX-M) and certain chromosomally-coded beta-lactamases of gram-negative bacteria. These beta-lactamases are present, for example, with *Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis* and *Haemophilus influenzae*. The spectrum of antibacterial action of ampicillin is broadened by bacteria whose beta-lactamases can be inhibited by sulbactam.

Relationship between pharmacokinetics and pharmacodynamics

The efficacy essentially depends on the length of time during which the active substance level of ampicillin is above the minimum inhibitory concentration (MIC) of the pathogen.

Mechanisms of resistance

A resistance to ampicillin/sulbactam can be based on the following mechanisms:

- Inactivation caused by beta-lactamases: ampicillin/sulbactam does not have sufficient activity against beta-lactamase-producing bacteria whose beta-lactamases are not inhibited by sulbactam.
- Reduced affinity of PBPs for ampicillin: The acquired resistance in pneumococci and other streptococci to ampicillin/sulbactam is based on modifications of existing PBPs resulting from a mutation. Methicillin (oxacillin)-resistant staphylococci are resistant due to their formation of an additional PBP with reduced affinity for ampicillin and all other beta-lactam antibiotics.
- In gram-negative bacteria, insufficient penetration of ampicillin through the outer cell wall can result in the PBPs not being sufficiently inhibited.
- Ampicillin can be actively transported out of the cell by means of efflux pumps.

A partial or complete cross-resistance of ampicillin/sulbactam exists with penicillins, cephalosporins as well as other beta-lactam/beta-lactamase-inhibitor combinations.

Breakpoints

Testing of ampicillin/sulbactam is carried by using a series of dilutions of ampicillin in the presence of a constant concentration of 4 mg/l sulbactam. The following MIC breakpoints were determined for susceptible and resistant pathogens:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 8 mg/l[N]	> 8 mg/l[N]
Staphylococcus spp. [1)]	- [1)]	- [1)]
Enterococcus spp.	≤ 4 mg/l	> 8 mg/l
Streptococcus spp. [2)]	- [2)]	- [2)]
Haemophilus influenzae	≤ 1 mg/l	> 1 mg/l
Moraxella catarrhalis	≤ 1 mg/l	> 1 mg/l
Gram-negative anaerobes	≤ 4 mg/l	> 8 mg/l
Gram-positive anaerobes	≤ 4 mg/l	> 8 mg/l
Non-species specific breakpoints [3)]*	≤ 2 mg/l	> 8 mg/l

[N] The National Antibiotics Sensitivity Test Committee for Germany established a breakpoint for the intermediary range for isolates of the following enterobacteria without a mechanism of resistance (wild type): *Citrobacter amalonaticus, Citrobacter koseri, Escherichia coli, Escherichia hermannii, Klebsiella* spp., *Proteus mirabilis, Proteus penneri, Proteus vulgaris, Raoultella* spp., *Salmonella* spp., *Shigella* spp., *Yersinia pseudotuberculosis*
I: >0.5 ≤ 8 mg/l.
This means that treatment of enterobacterial systemic infections with ampicillin/sulbactam requires a higher dose (e.g. 3x3 g IV in patients without modifying factors).

[1)] For *Staphylococcus* spp., the test result of cefoxitin was used. Methicillin (cefoxitin)-resistant staphylococci are considered resistant irrespective of the test result.

[2)] For *Streptococcus* spp. (groups A, B, C, G) and *Streptococcus pneumoniae*, the test result of penicillin G was used.

[3)] The breakpoint for the evaluation level susceptible refers to a daily intravenous dose of 3x3 g and the breakpoint for the evaluation level intermediary refers to a daily intravenous dose of 3x4 g.

* These are mainly based on the pharmacokinetics of serum levels.

Prevalence of acquired resistance in Germany

The prevalence of acquired resistance may vary geographically and over the course of time for individual species. Therefore, local information on the resistance situation is desirable – particularly for adequate treatment of severe infections. Expert advice on therapy should be sought if the local prevalence of resistance is such that the effectivity of ampicillin/sulbactam seems questionable. Particularly with serious infections or therapeutic failure, a microbiological diagnosis with identification of the pathogen and determination of its susceptibility to ampicillin/sulbactam should be sought.

Prevalence of acquired resistance in Germany based on data from national resistance surveillance projects and studies of the past 5 years (last updated: February 2018):

Commonly susceptible species
Aerobic gram-positive microorganisms
Enterococcus faecalis°
Staphylococcus aureus (methicillin-susceptible)
Streptococcus agalactiae°
Streptococcus pneumoniae (incl. penicillin-intermediate strains)°
Streptococcus pyogenes°
Streptococci of the "Viridans" group°^
Aerobic gram-negative microorganisms
Citrobacter koseri
Haemophilus influenzae
Moraxella catarrhalis Θ
Neisseria gonorrhoeae°
Anaerobic microorganisms
Bacteroides fragilis°
Gardnerella vaginalis°
Fusobacterium nucleatum°
Prevotella spp.°
Species for which acquired resistance may represent a problem in usage
Aerobic gram-positive microorganisms
Enterococcus faecium+
*Staphylococcus aureus*ɜ
Staphylococcus epidermidis+
Staphylococcus haemolyticus+
Staphylococcus hominis+
Aerobic gram-negative microorganisms
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris
Inherently resistant species
Aerobic gram-positive microorganisms
Staphylococcus aureus (methicillin-resistant)
Aerobic gram-negative microorganisms
Citrobacter freundii
Enterobacter cloacae
Legionella pneumophila
Morganella morganii
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia

Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum

° At the time of publication of this table no up-to-date data were available. In primary and standard literature and therapy recommendations susceptibility is assumed.

+ The resistance rate exceeds 50% in at least one region.

^ Collective term for a heterogenous group of streptococci species. Resistance rate may vary depending on the concerned streptococci species.

ϴ No up-to-date data available; in studies (older than 5 years), the proportion of resistant strains is given as < 10%

ɜ In the ambulatory sector, the resistance rate is around < 10%.

5.2 Pharmacokinetic properties

Following oral administration, sultamicillin is hydrolysed during absorption to provide sulbactam and ampicillin in a 1:1 molar ratio in the systemic circulation (375 mg sultamicillin are equivalent to 147 mg sulbactam and 220 mg ampicillin). Due to the esterification, a high oral bioavailability of both substances is achieved.

Peak serum levels of ampicillin after administration of Unasyn oral are approximately twice those of an equal dose of oral ampicillin.

The pharmacokinetic parameters after sultamicillin single doses in healthy subjects are contained in Table.

Table: Pharmacokinetic parameters after administration of single doses of sultamicillin in healthy subjects

Parameter	Sulbactam	Ampicillin
Half-life (h)	0.52 - 0.92	0.74 - 1.24
Recovery in the urine (% of dose)	42 - 86	42 - 92
Peak serum concentrations (mg/l)		
250 mg	2.6 - 3.6	2.6 - 4.0
375 mg	3.0	5.3
500 mg	5.1 - 6.9	8.0 - 8.7
750 mg	5.4 - 8.7	9.4 - 13.1
AUC (mg x h/l)		
250 mg	3.9 - 4.1	4.4 - 6.3
375 mg	5.2	9.3
500 mg	6.7 - 9.5	11.0 - 14.4
750 mg	9.7 - 13.2	14.7 - 21.8

Half-lives are prolonged in elderly patients and patients with impaired renal function. Also in premature infants and neonates, a reduced capacity for excretion of sultamicillin must therefore be anticipated. The dose should be reduced, if required (see section 4.2). However,

excretion of sulbactam and ampicillin is retarded likewise so that the concentration ratios of sulbactam and ampicillin remain constant.

Bioavailability
The absolute bioavailability of both sulbactam and ampicillin after oral administration of sultamicillin is approx. 80 to 85%. Previous intake of food does not influence the bioavailability of sultamicillin.

5.3 Preclinical safety data

Chronic toxicity studies have not produced any findings suggesting the emergence of hitherto unknown adverse effects in humans. Genotoxicity studies with ampicillin have not revealed any relevant evidence to suggest mutagenic or clastogenic potential. Long-term studies regarding the tumorigenic potential are not available. Embryotoxicity studies following intravenous administration to rats and rabbits revealed no evidence of teratogenic potential or other prenatal effects. Multiple-dose studies over up to 13 weeks in rats and dogs (2 mg/kg/day) have not revealed any effects on ovarian or testicular histology. Reversible spermatogenesis disorders have been reported in dogs following oral administration of 200 mg/day for 4 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Unasyn oral tablets
Lactose anhydrous, Corn starch dried, sodium starch glycolate, Hydroxypropyl cellulose, magnesium stearate

Unasyn powder for oral suspension
Sucrose, Xanthan Gum, Hydroxypropyl Cellulose, Carboxymethylcellulose Sodium, Citric acid anhydrous, Di-basic Sodium Phosphate anhydrous, Reynoseal Artificial Cherry Flavor.

6.2 Incompatibilities

Incompatibilities are unknown so far.

6.3 Shelf life

Do not use Unasyn Oral after the expiry date which is stated on the carton / bottle after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Unasyn oral tablets
Store at a temperature not exceeding 25 °C

Unasyn powder for oral suspension
Store at a temperature not exceeding 25 °C, in a dry place. After reconstitution to be used within 14 days when stored at temperature from 2-8°C.

6.5 Nature and contents of container(s)

Unasyn tablets

Carton box containing 2 (Aclar) blisters, each containing 6 tablets and an inner leaflet

Unasyn powder for oral suspension

Carton box containing plastic (HDPE) bottle containing (from 26.68 to 31.31 gm powder) covered with polypropylene (PP) screw on child resistant cap + inner leaflet

6.6 Special precautions for disposal (and other handling)

Keep out of the sight and reach of children.

Reconstitution instructions for Unasyn powder for oral suspension

Intake only after preparation of a suspension. For this purpose, the bottle with the powder for oral suspension should be filled with water up to the red marking line. It should be shaken immediately and vigorously until content is uniformly mixed, subsequently fill again up to the marking line and mix well. The suspension ready for use now can be used for 14 days if stored in the refrigerator.

Shake before each use!

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. MARKETING AUTHORISATION HOLDER

Pfizer Egypt Under license of Pfizer Inc., USA
–

8. MANUFACTURER

Pharco Pharmaceuticals for Pfizer Egypt
31 km Alexandria - Cairo Desert Road

9. DATE OF REVISION OF THE TEXT

April 2019

10. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists

Document Approval Record

Document Name:	Egypt_Sultamicillin and Sultamicillin tosylate (Unasyn)_ 375 mg Tab and 250 mg 5 ml POS _ LPD
Document Title:	MAH change

Signed By:	Date(GMT)	Signing Capacity
Abdelkhalek, Sara	14-Apr-2020 15:59:11	Regulatory Affairs Approval