Drug information

Generic name	Unasyn
common name	Ampicillin sodium, sulbactam sodium
European common name	Ampicillin Sodium, Sulbactam Sodium
Medicinal effect classification name	Antibiotic preparation containing β-lactamase inhibitor
Medicinal effect classification number	6139

Package insert information revised in January 2021 (19th edition)

Product information Composition / properties

Brand name	European trademark name	Manufacturing company	YJ code	Regulation classification
Unasyn-S for intravenous injection 0.75g	UNASYN-S for Intravenous Use	Pfizer	6139504 F1022	Prescription drugs
Unasyn-S 1.5g for intravenous injection	UNASYN-S for Intravenous Use	Pfizer	6139504 F2029	Prescription drugs
Unasyn-S for intravenous injection 3g	UNASYN-S for Intravenous Use	Pfizer	6139504 F3025	Prescription drugs

Contraindications

Do not administer to the following patients

Patients with a history of hypersensitivity to the ingredients of this drug

Patients with infectious mononucleosis [It has been reported that the administration of ampicillin caused a high frequency of rash.]

Contraindications in principle

In principle, it should not be administered to the following patients, but it should be administered with caution when it is particularly necessary.

Patients with a history of hypersensitivity to penicillin antibiotics

Efficacy / effect and usage / dose

Efficacy

<Applicable bacterial species>

Staphylococcus pneumoniae, Streptococcus pneumoniae, Moraxella (Branhamera) catarrhalis, Escherichia coli, Proteus, Haemophilus influenzae

<Indications>

Pneumonia, lung abscess, cystitis, peritonitis

Dosage

[For pneumonia, lung abscess, peritonitis]

In general, for adults, 6 g (titer) of sulbactam sodium / ampicillin sodium is intravenously or intravenously infused in two divided doses. In the case of severe infectious diseases, the dose can be increased as needed, but the upper limit is 3 g (potency) at a time, 4 times a day (12 g (potency) as a daily dose).

[In case of cystitis]

In general, for adults, 3 g (titer) of sulbactam sodium / ampicillin sodium is intravenously or intravenously infused in two divided doses.

Usually, for children, 60 to 150 mg (titer) / kg of sulbactam sodium / ampicillin sodium is intravenously or intravenously infused in 3 to 4 divided doses.

For intravenous injection, dissolve in Japanese Pharmacopoeia water for injection, Japanese Pharmacopoeia physiological saline or Japanese Pharmacopoeia glucose injection, and administer slowly.
For intravenous administration by infusion, it is dissolved in a replacement fluid before use.

Precautions related to dosage

When using this drug, in order to prevent the development of resistant bacteria, confirm β-lactamase-producing bacteria and ampicillin-resistant bacteria, and administer the drug for the minimum period necessary for the treatment of the disease.

When administering this drug to adult patients with severe renal impairment, administer it carefully, such as by adjusting the dose and interval of administration of this drug. [See "Careful administration" and "Pharmacokinetics"]

Precautions for use

Careful administration

Patients with a history of hypersensitivity to cephem antibiotics

Patients who are prone to allergic reactions such as bronchial asthma, rash, and urticaria to themselves, their parents, or their siblings

Patients with severe renal impairment [Refer to "Precautions related to dosage and administration" and "Pharmacokinetics"]

Patients with poor oral intake or parenteral nutrition, patients with poor general condition [Because bleeding tendency due to vitamin K deficiency may appear, observe carefully.]

Elderly [Refer to "Administration to the Elderly"]

Children under 1 year old [Refer to "Administration to children"]

Important basic notes

Since there is no reliable method for predicting the occurrence of shock and anaphylaxis caused by this drug, the following measures should be taken.

Ask sufficient questions about your medical history in advance. Be sure to check the history of allergies caused by antibiotics.

Before administration, be sure to prepare for emergency measures such as shock.

Patients should be kept at rest and closely monitored from the start of administration to the end of administration. In particular, observe carefully immediately after the start of administration.

When administering this drug, it is desirable to regularly test liver function, renal function, blood, etc.

When administering to children under 1 year of age, be careful of diarrhea and loose stools and administer with caution. [Refer to "Administration to children"]

Interaction

Interaction preface

Neither sulbactam nor ampicillin is metabolized, and it is excreted mainly in urine as an unchanged form. [See "Pharmacokinetics"]

Caution for combined use

Allopurinol	It has been reported that the incidence of rash increases when used in	Although the mechanism is unknown, drug-induced rash was observed in 22.4% of 67 inpatients who used allopurinol and ampicillin in combination, and in 7.5% of

	combination with ampicillin [1)] .	1,257 patients who took ampicillin alone. It has also been reported that 2.1% of 283 patients taking allopurinol without ampicillin experienced a drug-induced rash.
Anticoagulant	Penicillin injection may affect platelet aggregation and coagulation and enhance bleeding tendency.	The anticoagulant effect and the platelet aggregation inhibitory effect of penicillin injection may additively enhance the bleeding tendency.
Oral contraceptives	It has been reported that the contraceptive effect was diminished by the combined use with ampicillin.	This drug may alter the gut flora, which is thought to suppress the reabsorption of oral contraceptives by enterohepatic circulation.
Methotrexate	Combined use with penicillin may reduce methotrexate clearance.	Tubular secretion of methotrexate may be inhibited, its disappearance from the body may be delayed, and methotrexate toxicity may be enhanced.
Probenecid	The combined use may increase the blood concentration of this drug, prolong the half-life of the blood concentration, and increase the risk of toxicity of this drug.	The inhibitory effect of probenecid on tubular secretion may delay the excretion of this drug.

Side effects

Overview of side effect occurrence status

During development

Adverse reactions or abnormal laboratory test values were observed in 265 (16.64%) of the 1,593 general clinical studies and comparative clinical studies. Of these, side effects were 66 cases (4.14%), and the main ones were diarrhea (1.51%), rash (1.38%), fever (0.50%), etc. Abnormal laboratory test values were 217 cases (13.62%), and the main ones were ALT (GPT) increase (6.48%), AST (GOT) increase (6.02%), Al-P increase (1.62%), etc. [2) 3)] .

Post-marketing drug use-results survey (at the end of reexamination)

Side effects or abnormal laboratory test values were observed in 269 (7.54%) of 3,566 patients, and the main ones were liver dysfunction (2.89%), ALT (GPT) elevation (0.84%), and AST (GOT) elevation (0.81%).), Rash (0.67%), diarrhea (0.59%), etc.

General clinical study in which a daily dose of 12 g (titer) was administered (at the time of approval for partial changes in approval items)

In a general clinical study in which a daily dose of 12 g (titer) was administered to patients with moderate to severe community pneumonia, side effects or abnormal laboratory test values were observed in 10 of 47 patients (21.3%). Those were ALT (GPT) increase (10.6%), AST (GOT) increase (10.6%), Al-P increase (8.5%), γ-GTP increase (6.4%), diarrhea (4.3%), etc. [4)] .

Specific drug use-results survey in which a daily dose of more than 6 g (titer) was administered (at the end of reexamination regarding partial changes in approval items)

In a specific drug use-results survey of patients with pneumonia, pulmonary abscess and peritonitis, side effects or abnormal laboratory test values were observed in 96 of 980 patients (9.80%), mainly liver dysfunction (2.24%) and diarrhea (2.24%). 2.04%), rash (0.92%), AST (GOT) increase (0.82%), ALT (GPT) increase (0.61%), etc.

Serious side effects and side effect terms

Serious side effects

Shock, anaphylaxis

Since shock and anaphylaxis may occur, patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken (incidence unknown due to spontaneous reporting).

Toxic epidermal necrolysis (TEN), mucocutaneous ocular syndrome (Stevens-Johnson syndrome), acute generalized exanthematous pustulosis

Toxic epidermal necrolysis, mucocutaneous ocular syndrome, and acute generalized exanthematous pustule disease may occur. Patients should be carefully monitored. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. What to do (incidence unknown due to spontaneous reporting).

Blood disorder

Serious blood disorders such as agranulocytosis, anemia (including hemolytic anemia) (0.38%), and thrombocytopenia (0.19%) may occur. If any abnormalities are observed, take appropriate measures such as discontinuing administration (the frequency of agranulocytosis is unknown because it is a spontaneous report).

Acute kidney injury, interstitial nephritis

Serious renal disorders such as acute kidney injury (less than 0.1%) and interstitial nephritis may occur. Careful observation such as regular examinations should be performed, and if any abnormalities are observed, administration should be performed. Take appropriate measures such as discontinuing the treatment (interstitial nephritis is reported spontaneously, so the frequency is unknown).

Hemorrhagic colitis, pseudomembranous colitis

Serious colitis with bloody stools such as hemorrhagic colitis and pseudomembranous colitis may occur. If abdominal pain or frequent diarrhea occurs, take appropriate measures such as discontinuing administration immediately. (Frequency unknown due to spontaneous reporting).

Liver dysfunction

Liver dysfunction (0.10%) may occur, so observe carefully such as by conducting regular examinations, and if any abnormalities are observed, take appropriate measures such as discontinuing administration.

Interstitial pneumonia, eosinophilic pneumonia

Interstitial pneumonia (less than 0.1%) with fever, cough, dyspnea, chest X-ray abnormality, eosinophilic pneumonia, etc. may occur, so if such symptoms occur Discontinue administration and take appropriate measures such as administration of corticosteroids (the frequency of eosinophilic pneumonia is unknown because it is a spontaneous report).

Other side effects

	1 or more	0.1 to less than 1%	Less than 0.1%	Frequency unknown Note 1)
Skin Note 2)		Rash, itching	hives	Erythema multiforme
Blood Note 3)	Eosinophilia	Leukopenia		
liver	AST (GOT) rise, ALT (GPT) rise	Al-P rise, LAP rise, bilirubin level rise, γ-GTP rise	jaundice	
Digestive organ		Diarrhea / loose stool, nausea / vomiting	Abdominal discomfort	Black hairy tongue
Central nervous system				Neurological symptoms such as convulsions
Bacterial change				Mouth ulcer, candidiasis
Other		Fever	Vitamin K deficiency symptoms (hypoprothrombinemia, bleeding tendency, etc.)	Vitamin B group deficiency symptoms (glossitis, mouth ulcer, loss of appetite, neuritis, etc.)

Note 1: Frequency is unknown due to spontaneous reporting. Note 2: If this occurs, discontinue administration. Note 3: Carefully observe the patient by conducting regular

examinations, and if any abnormalities are observed, take appropriate measures such as discontinuing administration.

Administration to the elderly

For elderly patients, pay attention to the following points, pay attention to the dose and administration interval, and carefully administer the drug while observing the patient's condition.

In the elderly, the physiological function is generally deteriorated and side effects are likely to occur.

Elderly people may have a tendency to bleed due to vitamin K deficiency.

Administration to pregnant women, pregnant women, lactating women, etc.

Ampicillin and sulbactam have been reported to cross the placenta. Teratogenicity has been reported in rats with high doses of ampicillin (3,000 mg / kg / day), suggesting that the therapeutic benefit outweighs the risks for pregnant or potentially pregnant women. Administer only when determined.

Since it has been reported that it is transferred to breast milk5) , it is desirable not to administer it to lactating women, but if it is unavoidable, stop lactation.

Administration to children, etc.

Safety for low birth weight infants has not been established (less experience with use).

Safety for newborns has not been established (less experience with use).

Diarrhea and loose stools occur frequently in children under 1 year of age, so administration should be performed with caution.

Impact on laboratory test results

Note that administration of this drug may give false positive results in urine sugar tests using Benedict's reagent or Fehling's reagent.

Note that administration of ampicillin to pregnant women may result in a temporary decrease in serum levels of total bound estriol, estriol-glucuronide, bound estrone, and estradiol.

Overdose

High levels of β-lactam antibiotics in the cerebrospinal fluid may cause side effects of the nervous system, including convulsions. Therefore, if overdose is given to patients with renal impairment, hemodialysis is used from inside the body. To remove.

Precautions for application

At the time of preparation

Use immediately after dissolution (especially when dissolved in a sugar-containing solution such as glucose, fructose, xylitol, maltose, etc., the titer of ampicillin decreases, so use immediately and do not store).

At the time of administration

Intravenous administration may cause vascular pain, thrombosis or phlebitis, so pay close attention to the injection site, injection method, etc. and slow down the injection rate as much as possible.

It has been reported that the titer decreased when ampicillin and an aminoglycoside antibiotic preparation (dibekacin sulfate, arbekacin sulfate, etc.) were mixed as a compounding change.
When using in combination, pay attention to the administration method, such as changing the administration site and leaving an interval of 1 hour or more.

Pharmacokinetics

Serum concentration

Adult [6)]

The changes (average values) in serum concentrations of sulbactam and ampicillin when 0.75 g (titer) or 1.5 g (titer) of this drug were intravenously injected to 6 healthy adults by the crossover method are as shown in the figure below. Five minutes after intravenous injection, sulbactam was 18.7 μg / mL when 0.75 g (titer) was administered, 39.2 μg / mL was ampicillin, 40.0 μg / mL was sulbactam when 1.5 g (titer) was administered, and 78.8 μg / mL was ampicillin.
The half-lives (t1 / 2) of the concentrations of sulbactam and ampicillin were both about 1 hour, and the blood kinetics of both drugs were very similar.

Serum concentration when intravenously injected into adults

Children [2)]

The changes in serum concentration when 30 mg (titer) / kg of this drug was intravenously injected to 16 pediatric patients are shown in the figure below. The t1 / 2 of sulbactam and ampicillin is about 1 hour, which is blood in children. The kinetics was almost the same as in adults.

Serum concentration at the time of intravenous injection to pediatric patients

Urinary excretion and metabolism

When 0.75 g (titer) or 1.5 g (titer) of this drug was intravenously injected to 6 healthy adults, the urinary concentration (average value) 0 to 1 hour after administration was about 2,000 μg of sulbactam after administration of 0.75 g. When / mL and ampicillin were administered at about 4,000 μg / mL and 1.5 g, sulbactam was about 4,000 μg / mL and ampicillin was about 10,000 μg / mL, showing high values. The cumulative urinary excretion rate of sulbactam and ampicillin up to 24 hours after administration was about 80% for both sulbactam and ampicillin at 0.75 g and 1.5 g [6)] . Both sulbactam and ampicillin are hardly metabolized and are excreted mainly in urine as unchanged form [7)] .

Patients with renal dysfunction

According to overseas reports, t1 / 2 of sulbactam and ampicillin is prolonged in patients with moderate to severe renal function deterioration (10 cases) [8) 9)] .

Population pharmacokinetic analysis was performed using 222 plasma sulbactam and ampicillin concentration data obtained from 47 Japanese community-acquired pneumonia patients (creatinine clearance (CLcr): 34.6 to 176 mL / min). As a result, renal function (CLcr) is a significant variable factor in the clearance of sulbactam and ampicillin, and decreased renal function (CLcr) prolongs t1 / 2 of sulbactam and ampicillin, and the area under the concentration-time curve (AUC). Tends to rise. When the dosing intervals were adjusted as shown in the table below for patients with different renal functions, similar maximum concentrations (Cmax) and AUC estimates were obtained for all patients with renal dysfunction [10)] .

CLcr (mL / min)	Administration interval	Sulbactam			Ampicillin		
		Cmax (μg / mL)	AUC $_{0-48}$ (μg · h / mL)	$t_{1/2}$ (h)	Cmax (μg / mL)	AUC $_{0-48}$ (μg · h / mL)	$t_{1/2}$ (h)
90-60	4 times a day, every 6 hours	68.6-74.2	650-861	1.09 ~ 1.33	139-151	1260-1670	1.20 ~ 1.42
59-30	4 times a day, every 6 hours	74.4-85.1	872-1380	1.34 to 1.96	151-173	1690-2690	1.43 ~ 2.02
59-30	3 times a day, every 8 hours	73.3-81.5	655-1050	1.34 to 1.96	149-166	1270-2030	1.43 ~ 2.02
29-15	Twice a day, every 12 hours	79.5-86.4	718 to 1120	2.00 ~ 3.03	162-176	1400-2190	2.06 ~ 3.06
14-5	Once a day, every 24 hours	83.1-90.7	599 to 1190	3.16-6.28	170-185	1160-2310	3.20-6.27

Note: Pharmacokinetic parameters (lower and upper limits of PK parameters) obtained from plasma sulbactam and ampicillin concentration transition simulations when 3 g (titer) of this drug was intravenously infused over 30 minutes to patients with different renal functions. Corresponds to the upper and lower limits of the CLcr classification, respectively)

When administering to patients with restricted sodium intake, keep in mind that 1.5 g of unacin-S IV contains 115 mg (5 mEq) of sodium.

Intra-organizational migration

The bile concentrations of sulbactam and ampicillin when 1.5 g (titer) of this drug was intravenously injected into adult patients averaged 3.6 μg / mL and 19.8 μg / mL, respectively, 1 hour after intravenous injection [11)] .

Sputum of adult patients [12)] , intraperitoneal exudate [13)] , uterus, appendages tissue [14)] , pelvic death 腔滲 exudates [14)] , and cerebrospinal fluid of pediatric patients [15)], pus [16)] the transition to such the table below As shown, both sulbactam and ampicillin were found to be good.

Transition to body fluids and tissues

Body fluids / tissues	Dosage (titer)	Drug concentration (μg / mL or μg / g)	
		Sulbactam	Ampicillin
sputum	3g	2.40	1.50
Intraperitoneal exudate	1.5g	1.82	2.71
Uterus / accessories	1.5g	7.06 to 15.4	6.60-27
Pelvic dead space exudate	1.5g	11.6 to 16.4	19.1 to 21.6
Cerebrospinal fluid (pediatric)	100mg / kg	17.2	16.0
Pus (pediatric)	66.7 mg / kg	1.34	2.66

Clinical results

Clinical effect [2) 3) 4)]

General clinical trials and comparative clinical trials have been conducted, and the clinical effects by disease are as follows.
Of these cases, the clinical effects of β-lactamase highly producing bacteria detected by Staphylococcus, Escherichia coli, Proteus, and Haemophilus influenzae were 96.7% (29/30) for pneumonia / lung abscess and 88.9% (8/9) for peritonitis.), And cystitis was 89.2% (33/37).
The effective rate for pneumonia after administration of 12 g / day was 94.6% (35/37). The clinical effects by detected bacteria were 92.3% (12/13) for Streptococcus pneumoniae and 87.5% (7/8) for Moraxella (Branhamera) and Catarrhalis.

Clinical effects by disease

Disease name	adult			Children 60-150 mg / kg / day
	3g / day	4.5-6g / day	12g / day	
Pneumonia / lung abscess	162/196 (82.7%)	71/84 (84.5%)	35/37 Note) (94.6%)	212/215 (98.6%)
cystitis	141/200 (70.5%)	–	–	2/2 (100%)
peritonitis	30/36 (83.3%)	2/2 (100%)	–	–

Note: Clinical effect on pneumonia only (): Effective rate [more than effective]

Bacteriological effect [2) 3) 4)]

The bacterial elimination rate of 1,289 strains examined bacteriologically was 84.1% (1,084 / 1,289), and when this was limited to the applicable strains, the bacterial elimination rate was 86.9% (423/487) Note 1), and β-lactamase. In the case of highly produced strains, the elimination rate was 84.2% (123/146), which was almost the same. In addition, the bacterial elimination rate of 33 strains examined bacteriologically at the time of administration of 12 g / day was 84.8% (28/33), and 82.8% (24/29) Note 2) for

the applicable bacterial species. The bacterial elimination rate was 87.5% (7/8) only for the β-lactamase high-producing strains.
That is, it was shown that the effect on the β-lactamase high-producing strain is the same as that on the low-producing strain and the non-producing strain.

Bacteriological effects by dose

	3-6g / day	12g / day
Total isolates	1,084 / 1,289 (84.1%)	28/33 (84.8%)
Adaptation strain	423/487 (86.9%) Note 1)	24/29 (82.8%) Note 2)
Highly produced β-lactamase strain	123/146 (84.2%)	7/8 (87.5%)

Number of shares

Note 1: Staphylococcus, Escherichia coli, Proteus, Haemophilus influenzae

Note 2: In addition to Note 1, Streptococcus pneumoniae, Moraxella (Branhamera) Catarrhalis

Medicinal pharmacology

Antibacterial action

This drug exhibits strong antibacterial activity against β-lactamase production of Staphylococcus, Escherichia coli, Proteus, and Haemophilus influenzae, ampicillin-resistant bacteria, and Streptococcus pneumoniae [17) 18) 19)] .

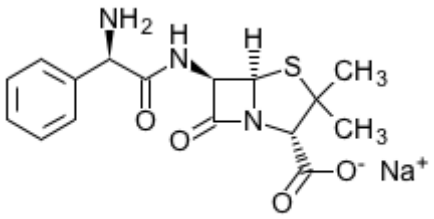
This drug shows a stronger therapeutic effect than ampicillin in a mouse single infection model by Staphylococcus, Escherichia coli, or Proteus, which is highly β-lactamase-producing [18)] .
In addition, it shows a stronger therapeutic effect than ampicillin in a mouse mixed infection model of ampicillin-resistant Haemophilus influenzae and ampicillin-sensitive Streptococcus pneumoniae, which are highly produced in β-lactamase [19)] .

Mechanism of action

Sulbactam strongly inactivates β-lactamase types Ic, II, III and IV, and mildly and irreversibly inactivates types Ia and V20 [)] , so ampicillin is hydrolyzed by these enzymes. It prevents and shows antibacterial activity against ampicillin-resistant bacteria. Ampicillin strongly inhibits the formation of peptidoglycan crosslinks in bacteria, hinders cell wall synthesis, and acts bactericidal [21)] .

Physicochemical knowledge about active ingredients

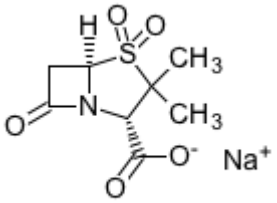
common name	Ampicillin sodium
Common name (European name)	Ampicillin Sodium
Abbreviation	ABPC

Chemical name	Monosodium (2S, 5R, 6R) -6- [(2R) -2-amino-2-phenylacetylamino] -3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2 -carboxylate
Molecular formula	$C_{16} H_{18} N_3 NaO_4 S$
Molecular weight	371.39
Properties	Ampicillin sodium is a white to pale yellowish white crystal or crystalline powder. Very soluble in water and slightly soluble in ethanol (99.5).
titer	The titer of sodium ampicillin indicates the amount of ampicillin ($C_{16} H_{19} N_3 O_4 S$) by mass (titer).
KEGG DRUG	 D02119

Physicochemical knowledge about active ingredients

common name	Sulbactam sodium
Common name (European name)	Sulbactam Sodium
Abbreviation	SBT
Chemical name	Monosodium (2S, 5R) -3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate 4,4-dioxide
Molecular formula	$C_8 H_{10} NNaO_5 S$
Molecular weight	255.22
Properties	Sulbactam sodium is a white to yellowish-white crystalline powder. It is freely soluble in water, sparingly soluble in methanol, extremely sparingly soluble in ethanol (99.5), and practically insoluble in acetonitrile.
titer	The titer of sodium sulbactam indicates the amount of sulbactam ($C_8 H_{11} NO_5 S$) by mass (titer).

KEGG DRUG



D02223

Packaging

Unasyn-S 0.75g for IV

10 vials

Unasyn-S 1.5g for IV

10 vials

Unasyn-S 3g for IV

10 vials

Work information

Revision history	Revised March 2019 Revised January 2021 (19th edition)
Document request destination	Please also request the in-house materials listed in "Main Documents" below. Pfizer, Inc. 151-8589 3-22-7 Yoyogi, Shibuya-ku, Tokyo Academic Information Dial 0120-664-467
Business format and trader name, etc.	Manufacture and sale Pfizer Japan Inc. 3-22-7 Yoyogi, Shibuya-ku, Tokyo