1.4 Product Information

1.4.1 Prescribing information (Summary of Product Characteristics)

1. Name of the medicinal product

Ampicillin for Injection 1.0g

2. Qualitative and quantitative composition

Ampicillin 1 g powder for solution for injection/infusion:

One vial contains 1063 mg of ampicillin sodium (equivalent to 1000 mg ampicillin).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for solution for injection/infusion

A White or almost white powder

4. Clinical particulars

4.1 Therapeutic indications

Ampicillin powder for solution for injection/infusion is indicated in the treatment of infections caused by ampicillin- sensitive organisms . As needed, ampicillin should be administered after initial broad spectrum coverage with a third generation cephalosporin.

• Complicated acute bacterial sinusitis

• Endocarditis

• Pyelonephritis

• Cystitis (see section 4.4)

• Intra-abdominal infections

• Female genital infections

• Listeria Meningitis when used in conjunction with an aminoglycoside

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

4.2 Posology and method of administration

Posology

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The dose level of ampicillin is dependent on the patient's age, weight and renal function, the severity and site of infection and the presumed or identified etiologic agents.

Adults and adolescents (over 12 years of age)

Intravenous or intra-muscular injection

1000MG every 4 to 6 hours (the daily dose can be increased to 6 g in case of severe infection)

Paediatric population (up to 12 years of age)

Intravenous injection or infusion

Child 1 month – 12 years

25mg/kg (max 1g) every 6 hours (the dose can be doubled in case of severe infection to 50 mg/kg (max 2 g) every 6 hours).

Neonate 21 – 28days

30mg/kg every 6 hours (the dose can be doubled in case of severe infection)

Neonate 7 – 21 days

30mg/kg every 8 hours (the dose can be doubled in case of severe infection)

Neonate under 7 days

30mg/kg every 12 hours (the dose can be doubled in case of severe infection)

Special populations

Renal Impairment

No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min. For severely impaired renal function with a glomerular filtration rate of 30 ml/min and less, a reduction in the dose is recommended, since an accumulation of ampicillin is to be expected:

- at a creatinine clearance of 20 to 30 ml/min, the normal dose should be reduced to ⅔,

- at a creatinine clearance below 20 ml/min, the normal dose should be reduced to ⅓. As a general

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rule, a dose of 1 g ampicillin in 8 hours should not be exceeded in patients with severe renal insufficiency.

Duration of treatment

The duration of use depends on the course of the disease. As a general rule, ampicillin is used for 7 to 10 days, but for at least another 2 to 3 days after the signs of disease have subsided.

For the treatment of infections with beta-haemolytic streptococci, for safety reasons it is recommended to extend the treatment to at least 10 days to prevent late complications (e.g. rheumatic fever, glomerulonephritis).

Method of administration

For intramuscular or intravenous use.

For intramuscular administration, the usual limit of the injection volume must be complied with. Intravenous injections must be given slowly over a 5-10 minute period. More rapid administration can lead to convulsions.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to any other penicillin 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) (see sections 4.4 and 4.8).

History of jaundice/hepatic impairment due to ampicillin..

4.4 Special warnings and precautions for use

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

The possibility of fungal and bacterial superinfections should be taken into account during treatment. In such case, the medicinal product should be discontinued and replaced with another

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suitable treatment. Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Ampicillin has a limited spectrum of antibacterial activity. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment with ampicillin. This particularly applies when considering the treatment of patients with intraabdominal infections, female genital infections and endocarditis. Ampicillin should be used in the treatment of cystitis only when susceptibility is documented..

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals.

Hypersensitivity and serum sickness-like reactions can be controlled with antihistamines and, if necessary, with systemic corticosteroids. If these types of reactions occur, ampicillin should be discontinued unless the doctor considers that the condition is life-threatening and can only be treated with ampicillin. Serious anaphylactic reactions require emergency treatment with adrenalin, oxygen and intravenous steroids.

Concomitant use of allopurinol during treatment with ampicillin can increase the likelihood of allergic skin reactions (see section 4.5).

Ampicillin should be avoided if infectious mononucleosis is suspected or the patient suffers from cytomegalovirus infection or lymphoid leukaemia since the occurrence of a morbilliform rash has been associated with this condition following the use of ampicillin.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

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

Prolongation of prothrombin time has been reported rarely in patients receiving ampicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

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Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

During treatment with Ampicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods (see section 4.5).

Antibiotic-associated colitis (caused in most cases by Clostridium difficile) has been reported with nearly all antibacterial agents including ampicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients presenting diarrhoea during or after the administration of any antibiotic (cases have been reported up to two months after the administration of antibacterial medicinal products). Should antibiotic-associated colitis occur, ampicillin should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation.

Ampicillin 1 g powder for solution for injection/infusion

10 ml of the reconstituted 10 % injection/infusion solution contains 2.86 mmol (65.8 mg) sodium. This should be taken into account in persons on a sodium-restricted (low- sodium/salt) diet.

4.5 Interaction with other medicinal products and other forms of interaction

Bacteriostatic antibiotics

Antagonism in regard to bacteriostatic antibiotics such as, for example, chloramphenicol and tetracycline.

Probenecid

The coadministration of probenecid inhibits the tubular secretion of ampicillin and leads to higher and longer persisting ampicillin concentrations in serum and bile.

Allopurinol

The simultaneous use of allopurinol during treatment with ampicillin can promote the development of allergic skin reactions

Anticoagulants

Coadministration of anticoagulants of the coumarin type can increase the tendency to bleeding.

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Digoxin

An increase in the absorption of coadministered digoxin is possible during ampicillin therapy.

Methotrexate

Ampicillin can inhibit the excretion of methotrexate and thereby intensify undesirable effects of methotrexate. The methotrexate levels in the blood should be monitored.

Glucose tests

In the case of high urine concentrations of ampicillin, false-positive urine-glucose reactions may occur if the copper reduction method is used. It is therefore recommended that glucose tests are based on enzymatic glucose oxidase reactions (see section 4.4)..

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of ampicillin in pregnant women. These data do not suggest that ampicillin has any adverse effects on pregnancy or the health of the foetus/newborn. No other relevant epidemiological data are available to date.

Animal studies do not indicate direct or indirect harmful effects respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of ampicillin during pregnancy. The treating doctor should consider whether the benefits to the pregnant woman outweigh the potential risks to the foetus.

Breast-feeding

Ampicillin is excreted in human milk and effects have been shown in breastfed newborns/infants of treated women. Breast fed infants may therefore suffer diarrhoea and mucosal yeast colonisation, which in some cases may necessitate the discontinuation of breast-feeding. The possibility of sensitisation should be considered. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ampicillin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

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In animal studies, ampicillin had no effect on fertility (see section 5.3).

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

Summary of the safety profile

The most commonly reported undesirable effects are skin reactions (pruritis, rash, exanthema, itching), abdominal pain, meteorism, soft stools, diarrhoea, nausea and vomiting.

People who have previously experienced hypersensitivity to penicillin and people with allergy, asthma, hay fever or urticaria in their medical history have a greater risk of hypersensitivity reactions.

Tabulated list of adverse reactions

The undesirable effects derived from clinical studies and post-marketing surveillance, sorted 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 (≥1/1,000 to ≤1/100)

Rare (≥1/10,000 to ≤1/1,000)

Very rare (≤1/10,000)

Not known (frequency cannot be estimated from the available data)

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System Organ Class	Preferred Term
Infections and infestations	
Uncommon	Infection with fungi or resistant bacteria especially during prolonged and/or repeated use
Blood and lymphatic system disorders	
Uncommon	Thrombocytopenia, anaemia, agranulocytosis, leukopenia, eosinophilia, thrombocytopenic purpura, haemolytic anaemia.
Very rare	Granulocytopenia, pancytopenia, Prolongation of bleeding and prothrombin time[1].
Immune system disorders [2,8]	
Uncommon	Serious allergic reactions such as serum sickness, allergic nephritis.
Rare	Life-threatening anaphylactic shock[6].
Not known	Hypersensitivity (see section 4.4)
Nervous system disorders[9]	
Rare	Dizziness, headache, myoclonus and seizures (in renal insufficiency or at very high intravenous doses).
Respiratory, thoracic and mediastinal disorders	
Uncommon	Laryngeal oedema
Gastrointestinal disorders	
Very common	Abdominal pain, nausea, vomiting, meteorism, soft stools, diarrhoea[7].
Uncommon	Enterocolitis, stomatitis, glossitis, pseudomembranous colitis[8] (in

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System Organ Class	Preferred Term
	most cases caused by Clostridium difficile)
Not known	Black hairy tongue
Skin and subcutaneous tissue disorders	
Very common	Pruritus, rash, exanthema, itching[3]
Common	Morbilliform rash[4], exanthema and enanthem in the oral region[5]
Uncommon	Angioneurotic oedema, allergic vasculitis, exfoliative dermatitis, exudative erythema multiforme, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis
Hepatobiliary disorders	
Uncommon	Transaminase elevation.
Musculoskeletal and connective tissue disorders	
Not known	Arthralgia
Renal and urinary disorders	
Uncommon	Crystalluria on high-dose intravenous administration, acute interstitial nephritis
Very Rare	Acute renal failure with excretion of urine crystals.
General disorders and administration site conditions	
Common	Swelling and pain, localised phlebitis.
Uncommon	Drug fever
Not known	Fever

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[1] See section 4.4

[2] See sections 4.3 and 4.4

[3] An immediate-type urticarial reaction generally suggests a true penicillin allergy and necessitates the interruption of treatment and institution of suitable medical measures. Medical advice should be sought regarding the future use of beta-lactam antibiotics.

[4] The typical, measles-like rash develops several (5 to 11) days after the start of treatment.

[5] The incidence of exanthem is higher in patients with infectious mononucleosis or lymphatic leukaemia.

[6] Allergic reactions are more likely to occur in patients with a tendency to allergies.

[7] These undesirable effects are usually mild in nature and frequently subside during, or otherwise after discontinuing the treatment.

[8] If there are signs of pseudomembranous colitis or severe hypersensitivity reactions, the treatment should be discontinued and medical treatment (see section 4.4) provided.

[9] If central nervous excitation, myoclonus or seizures occur, ampicillin should be discontinued and suitable treatment instituted.

Description of selected adverse reactions

Anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leucopenia and agranulocytosis have been reported during treatment with penicillins. These reactions are generally reversible after discontinuing treatment and are believed to be sensitisation phenomena. A moderate rise in serum concentration of aspartate aminotransferase (ASAT) has been observed, particularly in infants; however, the significance of these findings is unknown. Mild, temporary rises in ASAT have been observed in people who receive larger (two to four times) and more frequent intramuscular injections than usual. Information indicates that ASAT is released at the administration site of the intramuscular injection of ampicillin sodium and that the presence of an increased amount of this enzyme in the blood is not necessarily a sign that the liver is affected

4.9 Overdose

Symptoms

Typical signs of intoxication following the administration of larger amounts of ampicillin have not been observed to date. Long-term therapy is also not associated with specific toxic adverse reactions.

Toxic reactions can include nausea, vomiting, diarrhoea, electrolyte disorders, altered consciousness, coma, haemolytic reactions and acidosis.

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The single administration of a larger amount of ampicillin is not acutely poisonous (toxic).The administration of very high doses can lead to oliguric renal failure and may have effects on nerve cells, for example in the form of central nervous excitation, impairments of muscular function and seizures. The risk of these undesirable effects is increased in patients with severely impaired renal function. In individual cases, however, these effects were only observed after intravenous administration.

Management

In the event of an overdose, the treatment should be discontinued. There is no specific antidote in the event of overdose. Treatment comprises symptomatic measures with particular attention to maintaining the water/electrolyte balance.

Ampicillin can be removed from the body by haemodialysis but not via peritoneal dialysis

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Antibacterials for systemic use, penicillins with extended spectrum

ATC code: J01CA01.

Mechanism of action

The mechanism of action of ampicillin is based on inhibition of bacterial wall synthesis (in the growth phase) via blockade of the penicillin-binding proteins (PBPs) such as the transpeptidases. This results in a bactericidal action.

PK/PD relationship

The efficacy depends mainly on the time period for which the active substance level of ampicillin remains above the minimal inhibitory concentration (MIC) of the microorganism.

Mechanisms of resistance

Resistance to ampicillin can be due to the following mechanisms:

-Inactivation by beta-lactamases: ampicillin has only low beta-lactamase stability and is therefore not active against beta-lactamase forming bacteria. Almost all strains of some bacterial species form beta-lactamases. These species are therefore naturally resistant to ampicillin (e.g.

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Enterobacter cloacae, Klebsiella pneumoniae).

-Reduced affinity of PBPs for ampicillin: the acquired resistance of pneumococci and other streptococci is due to the modification of existing PBPs as the result of a mutation. Methicillin (oxacillin)-resistant staphylococci, however, are resistant due to the formation of an additional PBP with reduced affinity for ampicillin.

-Insufficient penetration of ampicillin through the outer cell wall of gram-negative bacteria can result in inadequate inhibition of the PBPs.

-Ampicillin can be actively extruded from the cell by efflux pumps.

Partial or complete cross-resistance of ampicilllin exists with amoxicillin and to some extent with other penicillins and cephalosporins.

Breakpoints

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

Microorganism	**Susceptible ≤**	**Resistant ≥**
Enterobacteriaceae	≤ 8 mg/l	≥ 8 mg/l
Enterococcus spp.[1]	≤ 4 mg/l	≥ 8 mg/l
Haemophilus influenzae	≤ 1 mg/l	≥ 1 mg/l
Staphlococcus spp[2]	≤ 0.12 mg/l	≥ 0.12 mg/l
Streptococcus A, B, C G[2]	≤ 0.25 mg/l	≥ 0.25 mg/l
Streptococcus pneumoniae	≤ 0.5 mg/l	≥ 2 mg/l
Other streptococci[1]	≤ 0.5 mg/l	≥ 2 mg/l
Neisseria meningitidis	≤ 0.12 mg/l	≥ 1 mg/l
Gram-negative anaerobes	≤ 0.5 mg/l	≥ 2 mg/l
Gram-positive anaerobes	≤ 4 mg/l	≥ 8 mg/l

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Non species-specific limit values	≤ 2 mg/l	≥ 8 mg/l
Listeria monocytogenes	≤ 1 mg/l	≥ 1 mg/l

[1]In endocarditis, refer to national or international endocarditis guidelines for breakpoints.
[2]Breakpoints values are based on benzylpenicillin breakpoints

Susceptibility
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infection is questionable.

Commonly susceptible species
Aerobic gram-positive microorganisms
Enterococcus faecalis
Staphylococcus aureus (methicillin-sensitive)
Streptococcus agalactiae
Streptococcus pneumoniae (incl. penicillin-intermediate strains)
Streptococcus pyogenes
Streptococci of the "Viridans group ^
Anaerobic microorganisms
Bacteroides fragilis°
Fusobacterium nucleatum°
Other microorganisms
Gardnerella vaginalis°

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Species for which acquired resistance may be a problem
Aerobic gram-positive microorganisms
Enterococcus faecium[+]
Staphylococcus aureus[+]
Staphylococcus epidermidis[+]
Staphylococcus haemolyticus[+]
Staphylococcus hominis[+]
Aerobic gram-negative microorganisms
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Moraxella catarrhalis[+]
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Anaerobic microorganisms
Prevotella spp.
Inherently resistant organisms
Aerobic gram-positive microorganisms
Staphylococcus aureus (methicillin-resistant)
Aerobic gram-negative microorganisms
Acinetobacter baumannii
Citrobacter freundii
Enterobacter cloacae
Klebsiella pneumoniae
Morganella morganii
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia
Anaerobic microorganisms
Bacteroides spp.
Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Legionella pneumophila
Mycoplasma spp.
Ureaplasma urealyticum

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° No current data were available when the table was published. Sensitivity is assumed in the primary literature, standard works and therapy recommendations.
+ The resistance rate is above 50% in at least one region.
^ Collective name for a heterogeneous group of *Streptococcus* species. Resistance rate can vary depending on the *Streptococcus* species concerned.
∞ No recent data available; in studies (older than 5 years) the proportion of resistant strains is reported as ≥10%.
³ The resistance rate is <10% in the outpatient setting.

5.2 Pharmacokinetic properties

Distribution

Ampicillin is extensively distributed to tissues, crosses the placental barrier and diffuses into breast milk. Only 5 % of the ampicillin concentration in plasma diffuses into cerebrospinal fluid (CSF) with intact meninges. With inflamed meninges, the ampicillin concentration in CSF can increase to 50 % of the ampicillin concentration in plasma.

The serum protein binding is 17-20 %. The apparent volume of distribution is about 15 L.

Higher concentrations of the active form are observed in bile than in serum.

Serum level

After oral administration of 1000 mg ampicillin, peak plasma levels of about 5 mg/l are reached after 90 to 120 min. After intramuscular injection, peak plasma levels are reached after 30 to 60 min.

Biotransformation

Ampicillin is partly metabolised to microbiologically inactive penicilloates.

Elimination

Ampicillin is eliminated intact mainly by the renal route, but also through bile and faeces. After oral administration, about 40 % of a dose is recovered unchanged in the urine. After parenteral administration, about 73 +/- 10 % of an administered dose is excreted as unchanged substance in the 0- to 12-hour urine. Up to 10 % of a dose is eliminated in the form of biotransformation products. The elimination half-life is About 50 to 60

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min. In oliguria, the half-life may be prolonged to 8 to 20 hours. The half-life is also prolonged in newborns (2 to 4 hours). The renal clearance of ampicillin is About 194 ml/min after intravenous administration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies repeated-dose toxicity and genotoxicity.

Following intravenous administration no teratogenic potential or pre-natal effects were observed in the rat or rabbit. Repeated administration for up to 13 weeks in the rat and dog (2 mg/kg/day) showed no histological effects on the ovary; however, reversible impairment of spermatogenesis was observed in the dog at 200 mg/day. In animal studies at doses higher than those used in humans, ampicillin did not have any adverse effects on fertility.

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

Ampicillin solutions should always be administered separately, unless compatibility with other infusion solutions or medicines has been established.

This medicinal product must not be mixed with other solutions except those mentioned in section 6.6.

Ampicillin solutions should not be mixed with aminoglycosides, metronidazole and injectable tetracycline derivatives such as oxytetracycline, rolitetracycline and doxycycline. Visual signs of incompatibility are precipitation, clouding and discoloration.

6.3 Shelf life

36 months.

Shelf-life after preparation of the ready-to-use solution

Reconstituted/diluted solution should be used immediately.

6.4 Special precautions for storage

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Ampicillin should not be stored above 30°C.

Use only freshly prepared solutions.

6.5 Nature and contents of container

7mL Type II glass vial with Al-cap, 50vials/tray/middle box,20 middle boxes/carton.

6.6 Special precautions for disposal and other handling

Ampicillin solutions are compatible with 0.9% (9 mg/ml) sodium chloride solution, 5% (50mg/ml) glucose solution and Ringer solution.

Ampicillin 1 g powder for solution for injection/infusion

The 10 % injection/infusion solution is prepared by dissolving 1.06 g powder in 10 ml water for injections.

The solutions should always be prepared freshly before use and checked for clarity. Use only clear solutions for injection or infusion! Do not use solutions with cloudiness or precipitation.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Reyoung Pharmaceutical Co., Ltd

No.1 Ruiyang Road, Yiyuan County Shandong, P.R. China.

8. Marketing authorisation number(s)

Lu 20160062

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 11/06/2014

10. Date of revision of the text

01/01/2016

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