SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Co-amoxiclav 1000mg/200mg Powder for Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1000mg amoxicillin (as sodium salt) and 200mg clavulanic acid (as potassium salt).

Each ml of reconstituted solution contains 50mg amoxicillin (as sodium salt) and 10mg clavulanic acid (as potassium salt). Refer to section 6.6 for the method of reconstitution.

Each 1.2g vial of co-amoxiclav contains 1.0mmol of potassium and 3.1mmol of sodium (approx).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

Co-amoxiclav 1000mg/200mg Powder for Solution for Injection or Infusion is a white or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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Treatment of the following bacterial infections when caused by amoxicillin-resistant but amoxicillin-clavulanate susceptible organisms (see section 5.1):

Upper and Lower Respiratory Tract Infections, including:

• otitis media

• acute sinusitis

• acute exacerbations of chronic bronchitis

• community-acquired pneumonia

Upper and Lower Urinary Tract Infections

Skin and Soft Tissue Infections

Genito-Urinary Tract Infections including septic abortion, pelvic or puerperal sepsis, intra-abdominal sepsis

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

4.2 Posology and method of administration

Dosages for the treatment of infection

Adults and children over 12 years

Usually 1.2g eight hourly. In more serious infections, increase frequency to six-hourly intervals.

Children 3 months – 12 years

Usually 30mg/kg* co-amoxiclav eight hourly. In more serious infections, increase frequency to six-hourly intervals.

Children 0-3 months

30mg/kg* co-amoxiclav every 12 hours in premature infants and in full-term infants during the perinatal period, increasing to eight hours thereafter.

*Each 30mg co-amoxiclav provides 25mg of amoxicillin and 5mg of clavulanic acid.

Each 1.2g vial of co-amoxiclav contains 1.0mmol of potassium and 3.1 mmol of sodium (approx).

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Adult dosage for surgical prophylaxis

The usual dose is 1.2g co-amoxiclav injection given at the induction of anaesthesia. Operations where there is a high risk of infection, e.g. colorectal surgery, may require three, and up to four doses of 1.2g of co-amoxiclav injection in a 24 hour period. These doses are usually given at 0, 8, 16 (and 24) hours. This regimen can be continued for several days if the procedure has a significantly increased risk of infection.

Clear clinical signs of infection at operation will require a normal course of intravenous or oral co-amoxiclav therapy post-operatively.

Dosage in renal impairment

Adults

Mild impairment (creatinine clearance>30 ml/min): No change in dosage.

Moderate impairment (creatinine clearance 10-30 ml/min): 1.2g IV stat., followed by 600mg IV 12 hourly.

Severe impairment (creatinine clearance <10 ml/min): 1.2g IV stat., followed by 600mg IV 24 hourly. Dialysis decreases serum concentrations of co-amoxiclav and an additional 600mg IV dose may need to be given during dialysis and at the end of dialysis.

Children

Similar reductions in dosage should be made for children.

Dosage in hepatic impairment

Dose with caution. Monitor hepatic function at regular intervals. There are, as yet, insufficient data on which to base a dosage recommendation.

Each 1.2g vial of co-amoxiclav contains 1.0mmol of potassium and 3.1 mmol of sodium (approx).

Co-amoxiclav may not be used in patients with severe hepatic impairment and in patients in whom hepatic functional impairment has occurred on previous therapy with co-amoxiclav (see section 4.3 and 4.4). Liver function parameters should be checked at regular intervals in patients with signs of hepatic lesions and a change of therapy should be given considerations if these parameters exacerbate on treatment.

Administration

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Co-amoxiclav injection may be administered either by intravenous injection or by intermittent infusion. Therapy can be started parenterally and continued with an oral preparation.

Co-amoxiclav Injection should be given by slow intravenous injection over a period of three to four minutes and used immediately after reconstitution. It may be injected directly into a vein or via a drip tube.

Alternatively, co-amoxiclav intravenous may be infused in Water for Injections Ph Eur or Sodium Chloride Intravenous Injection BP (0.9% w/v). Add, without delay, 600 mg reconstituted solution to 50 ml infusion fluid or 1.2 g reconstituted solution to 100 ml infusion fluid (e.g. using a minibag or in-line burette). Infuse over 30-40 minutes and complete within four hours of reconstitution.

Any residual antibiotic solutions should be discarded.

Co-amoxiclav Injection is less stable in infusions containing glucose, dextran or bicarbonate. Reconstituted solution should, therefore, not be added to such infusions but may be injected into the drip tubing over a period of three to four minutes.

It is not suitable for intramuscular administration. Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

4.3 Contraindications

Hypersensitivity to the constituents, amoxicillin and clavulanic acid. Penicillin hypersensitivity. Attention should be paid to possible cross-sensitivity with other β-lactam antibiotics, e.g. penicillins, cephalosporins, carbapenems, monobactams due to the danger of anaphylactic shock. Consequently a careful history should be taken in regard to allergic reaction before commencing treatment. Co-amoxiclav should not be given to patients with a verified hypersensitivity to any beta-lactam drug.

A previous history of co-amoxiclav or penicillin-associated jaundice/hepatic dysfunction.

Co-amoxiclav may not be used in patients with severe hepatic impairment and in patients in whom hepatic functional impairment has occurred on previous therapy with co-amoxiclav, for example cholestatic jaundice induced by co-amoxiclav or penicillin.

Patients with infectious mononucleosis (glandular fever) and patients with lymphatic leukaemia have a higher risk of exanthema and consequently co-amoxiclav injection should not be administered during these diseases to treat concomitant bacterial infections.

4.4 Special warnings and precautions for use

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Although severe allergic reactions are more likely in patients who have experienced beta-lactam hypersensitivity, these may occur in the absence of any such history. In such cases treatment should be discontinued immediately and appropriate management instituted.

Co-amoxiclav should be used with caution in patients with allergic diathesis, including asthma, since such patients may have a higher risk of allergic reactions to co-amoxiclav.

Patients with evidence of hepatic dysfunction should be treated with caution. Liver function parameters should be monitored in patients with signs or symptoms of hepatic impairment. Discontinuation of therapy should be considered in case of deterioration of liver function parameters during treatment.

In patients with renal impairment, excretion of co-amoxiclav will be delayed and depending on the degree of the impairment, it may be necessary to reduce the total daily dosage (see section 4.2).

In long term use (more than 10-14 days), regular monitoring of renal and hepatic function is recommended.

Prolonged use of co-amoxiclav, or other broadspectrum antibiotics, may lead to superinfections due to an overgrowth of non-susceptible organisms and yeasts.

In case of severe and persistent diarrhoea, the possibility of pseudomembraneous colitis must be considered, in which case therapy should be discontinued.

The presence of high urinary concentrations of amoxicillin can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals.

At high doses, adequate fluid intake and urinary output must be maintained to minimise the possibility of amoxicillin crystalluria.

4.5 Interaction with other medicinal products and other forms of interaction

Other bacterial agents: There is a possibility that the antibacterial action of amoxicillin could be antagonised on co-administration with macrolides, tetracyclines, sulphonamides or chloramphenicol.

Probenecid : By inhibiting the renal elimination of amoxicillin (but not clavulanic acid) the concomitant administration of probenecid leads to an increase in the concentrations of amoxicillin in serum and bile.

Allopurinol : Concomitant administration of allopurinol may promote the occurrence of allergic cutaneous reactions.

Digoxin: An increase in the absorption of digoxin is possible on concurrent administration with amoxicillin.

Co-amoxiclav / disulfiram : Co-amoxiclav should not be used concurrently with disulfiram.

Methotrexate : Concomitant administration with methotrexate may lead to an increase in toxicity of methotrexate.

Anticoagulants: Concomitant administration of amoxicillin and coumarin anticoagulants, such as warfarin, may increase the incidence of bleeding.

Oral hormonal contraceptives: Administration of amoxicillin can transiently decrease the plasma level of oestrogens and progesterone and may reduce the efficacy of oral contraceptives. Patients should be advised to use supplemental non-hormonal contraceptive measures.

Other forms of interaction: Amoxicillin may produce false positive results in glucose determination tests and tests for urobilinogen performed with nonenzymatic methods. Likewise the urobilinogen test can be affected.

Amoxicillin may decrease the amount of urinary estriol in pregnant women. Diarrhoea may decrease the absorption of other drugs and consequently have a negative influence on their effectivity.

Forced diuresis will lead to an increased elimination of amoxicillin resulting in decreased serum concentrations.

4.6 Pregnancy and lactation

Reproduction studies in animals (mice and rats) with orally and parenterally administered co-amoxiclav have shown no teratogenic effects. There is limited experience of the use of co-amoxiclav in human pregnancy. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Co-amoxiclav may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 Effects on ability to drive and use machines

Co-amoxiclav may sometimes be associated with side effects (such as rarely dizziness and even less often convulsions) that may impair the ability to drive a vehicle, to operate machinery and/or work safely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions are hypersensitivity reactions:

Common (1% but < 10%)

Cutaneous reactions such as exanthema, pruritus, urticaria; the typical morbilliform exanthema occurs 5-11 days after start of therapy. Immediate appearance of urticaria indicates an allergic reaction to amoxicillin and therapy should therefore be discontinued.

Rare (0.01% but < 0.1%): (see also section 4.4)

• Angioneurotic oedema (Quincke's oedema)

• Erythema multiforme syndrome

• Stevens-Johnson syndrome

• Eosinophilia

• Drug fever

• Laryngeal oedema

• Serum sickness

• Haemolytic anaemia

• Allergic vasculitis

• Interstitial nephritis

• Anaphylactic shock

Other possible side effects:

Blood disorders:

There have been isolated reports of leucopenia, granulocytopenia, thrombocytopenia, pancytopenia, anaemia, myelosuppression, agranulocytosis, prolongation of bleeding time and prolongation of prothrombin time. However, these changes were reversible on discontinuation of therapy.

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Gastrointestinal disorders:

Common (1% but < 10%):

Gastric complaints, nausea, loss of appetite, vomiting, flatulence, soft stools, diarrhoea, enanthemas (particularly in the region of the mouth), dry mouth, taste disturbances. These effects on the gastrointestinal system are mostly mild and frequently disappear either during the treatment or very soon after completion of therapy. The occurrence of these side-effects can generally be reduced by taking amoxicillin during meals or with some food. If severe and persistent diarrhoea occurs, the rare possibility of pseudomembraneous colitis should be considered. The administration of anti-peristaltic drug is contraindicated.

Very rare (< 0.01%)

Development of a black tongue.

Liver disorders:

Uncommon (0.1% but < 1%):

Moderate and transient increase of liver enzymes. Rare reports of hepatitis and cholestatic jaundice.

CNS disorders:

CNS effects have been seen rarely. They include hyperkinesia, dizziness and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Renal disorders

Uncommon (0.01% but < 0.1%):

Acute interstitial nephritis may occur in rare cases.

Other undesirable effects

Prolonged and repeated use of the preparation can result in superinfections and colonisation with resistant organisms or yeasts such as oral and vaginal candidiasis.

4.9 Overdose

Symptoms of overdosage

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In the event of overdosage, gastrointestinal symptoms, such as nausea, vomiting and diarrhoea and disturbances of the fluid and electrolyte balance are possible. Also, convulsions may exist.

Management of overdosage

There is no specific antidote for overdose. Treatment consists of haemodialysis and symptomatic measures paying particular attention to the water and electrolyte balance, especially if there are any gastro-intestinal symptoms. Administration of medicinal charcoal and gastric lavage are useful only in cases of very high overdose (> 250mg/kg). In case of severe renal insufficiency, Co-amoxiclav can be eliminated from the circulation via haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antibiotic/chemotherapeutic (penicillin with broad spectrum of action) (JOICR).

Mechanism of Action

Amoxicillin:

Amoxicillin is an acid-stable aminopenicillin that is susceptible to hydrolysis by common β-lactamase enzymes.

Clavulanic acid:

Clavulanic acid is a β-lactam molecule that is able to inhibit many of the most commonly occurring β-lactamases such as staphylococcal penicillinases and enzymes of the TEM, OXA, SHV families (including many of the extended spectrum β-lactamases of these groups). Thus, combination of amoxicillin with clavulanic acid maintains the activity of the aminopenicillin against organisms that produce sufficient quantities of these enzymes that would otherwise render inactive.

However, clavulanic acid is not able to inhibit the AmpC (Class 1) β-lactamases that may be produced by certain Gram-negative bacilli or the metallo-β-lactamases (such as carbapenemases). Therefore, organisms that are normally susceptible to amoxicillin but have acquired the ability to produce any if these enzymes in amounts sufficient to render amoxicillin inactive would not be susceptible to Co-amoxiclav.

Antibacterial Spectrum

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MIC Breakpoints

The MIC breakpoints according to the NCCLS criteria and methodology that separates susceptible (S) organisms from those that are immediately susceptible (I) or resistant (R) are:

• Enterobacteriaceae : S 8/4 mg/L

I = 16/8 mg/L

R 32/16 mg/L

• Staphylococci : S 4/2 mg/L

R 8/4 mg/L

• Haemophilus influenzae : S 4/2 mg/L

R 8/4 mg/L

• Streptococcus pneumoniae: S 0.5/0.25 mg/L

I = 1/0.5 mg/L

R 2/1 mg/L

BSAC criteria are as follows (Expressed as amoxicillin) :

• Enterobacteriaceae: S 8mg/L

R 16 mg/L

• In UTI: S 32mg/L

R 64 mg/L

• Haemophilus influenzae,

Moraxella catarrhalis: S 1 mg/L

R 2 mg/L

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Spectrum of action of Co-amoxiclav

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. This information gives only approximate guidance on the probabilities whether micro-organisms will be susceptible to Co-amoxiclav or not. As far as possible the information on the European range of acquired resistance for the individual micro-organism is indicated in brackets.

Micro-organisms Resistance prevalence in the EU*

SUSCEPTIBLE

Gram-positive aerobes

E.faecalis

S.aureus methicillin-susceptible

S.pneumoniae 0% - 26%*

S.pyogenes

Gram-negative organisms

E.coli 5 – 20% *

K.pneumoniae 7% *

H.influenzae 2%

M.catarrhalis

P.mirabilis

N.gonorrhoeae Up to 34% *

Anaerobes

B.fragilis

C.perfringens

Peptostreptococcus spp

RESISTANT

Gram-positive organisms

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E.faecium

S.aureus methicillin-resistant

Gram-negative organisms

E.aerogenes

E.cloacae

M.morganii

P.aeroginosa

Serratia spp.

P.rettgeri

Others

Legionellae

Chlamydia spp.

Mycoplasma spp.

Ricketsia spp.

* It is recommended that local information on the epidemiology of resistant micro-organisms should be consulted.

Resistance

Organisms that are normally resistant to amoxicillin by non-beta-lactamase-mediated mechanisms (such as impermability, altered penicillin-binding proteins or drug efflux pumps) or via the manufacture of enzymes that are not inhibited by clavulanic acid would also be resistant to amoxicillin/clavulanate.

5.2 Pharmacokinetic properties

Amoxicillin:

The absolute bioavailability of amoxicillin depends on the dose and ranges between approximately 72 and 94%. Absorption is not affected by intake of food. Peak plasma concentrations are present about 1 to 2 hours after administration of amoxicillin. The apparent distribution volume ranges between approximately 0.3 and 0.4 l/kg and binding to

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serum proteins is approximately 17 – 20%. Amoxicillin diffuses through the placental barrier and a small fraction is excreted into breast milk.

Amoxicillin is largely excreted through the kidneys (52 ± 15% of a dose in unchanged form within 7 hours) and a small fraction is excreted in the bile. Total clearance ranges between approximately 250 and 370 ml/min. The serum half-life of amoxicillin in subjects with intact renal function is approximately 1 hour (0.9 – 1.2h), in patients with creatinine clearance ranging between 10 and 30ml/min it is about 6 hours and in anuria it ranges between 10 and 15 hours.

Clavulanic acid:

The absolute bioavailability of clavulanic acid of approximately 60% differs markedly from individual to individual. Absorption is not affected by intake of food. Peal concentrations of clavulanic acid are present after approximately 1 to 2 hours. The apparent distribution volume is about 0.2 l/kg and the serum protein binding rate is approximately 22%. Clavulanic acid diffuses through the placental barrier. No exact data are as yet available in regard to excretion into breast milk.

The substance is partly metabolised (approximately 50 – 70%) and is about 40% is eliminated through the kidneys (18 – 38% of the dose is unchanged form). The total clearance is approximately 260 ml/min. The serum half-life of clavulanic acid in subjects with intact renal function is approximately 1 hour, in patients with creatinine clearance ranging from 20 and 70ml/min it is approximately 2.6 hours and in anuria it ranges between 3 and 4 hours.

Pharmacologically relevant pharmacokinetic interaction between amoxicillin and clavulanic acid have not been observed so far. Both amoxicillin and clavulanic acid are haemodialysable.

5.3 Preclinical safety data

a) Acute toxicity

Investigations of the acute toxicity (LD50) of amoxicillin and clavulanic acid in adult animals and neonates have confirmed very low toxicity potential. The LD50 of clavulanic acid (potassium salt) is determined by the potassium content.

Administration of clavulanic acid (potassium salt) together with amoxicillin does not result in any unexpected or synergistic toxicity.

b) Chronic toxicity / subchronic toxicity

Extensive studies of the chronic toxicity have been carried out based on international standards. Solely after high doses (corresponding to 20- to 50- fold the maximal human dose) were mild haematological and blood-chemical changes observed which regressed completely following discontinuation of the therapy.

c) Mutagenic and tumorigenic potential

In-vitro and in-vivo studies did not reveal any signs of any mutagenic effects of the combination of amoxicillin and clavulanic acid.

d) Reproductive toxicity

After treatment of various infections in pregnant women (approximately 560 pregnancies) with Co-amoxiclav no increased occurrence of malformations was observed. Amoxicillin and clavulanic acid diffuse through the placenta and are excreted into breast milk (probable elimination of clavulanic acid into breast milk).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Co-amoxiclav Injection should not be mixed with blood products, other proteinaceous fluids such as protein hydrolysates or with intravenous lipid emulsions.

If co-amoxiclav is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

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

6.3 Shelf life

As packed for sale: 3 years.

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Use the reconstituted solution immediately. Discard any unused solution.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear glass vials (Ph.Eur Type II) with a chlorobutyl stopper and aluminium-propylene flip-off cap.

6.6 Special precautions for disposal and other handling

To reconstitute dissolve in 20 ml Water for Injections Ph Eur or Sodium Chloride Intravenous Injection BP (0.9% w/v) (Final volume 20.9 ml.).

For single use. Discard any unused product immediately after use.

7. MARKETING AUTHORISATION HOLDER

HARBIN PHARMACEUTICAL GROUP CO., LTD

General Pharm. Factory

No.109 Xuefu Road Nangang Dist, Harbin city

People Republic of China

8. DATE OF REVISION OF THE TEXT

APR. 2021

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