CLAVOSPEY

Instructions for the medicinal product

Composition: Each vial contains:
Sterile Amoxicillin Sodium BP equivalent to Amoxicillin 1.0 g
Sterile Potassium Clavulanate BP equivalent to Clavulanic Acid 0.2 g

Product Description:
Physical properties: White color Crystelline powder, 1.2 g in 20 ml Clear Glass Vial.
Chemical name: Amoxicillin Sodium & Potassium Clavulanate.
Molecular weight: 387.385989 g/mol & 237.25112 g/mol.
Empirical / Structural formula: C16H18N3NaO5S & C8H8KNO5.

ATC code: J01CR02.

Pharmacodynamics:
Clavospey is a combination of amoxicillin and potassium clavulanate. The amoxicillin component of the formulation exerts a bactericidal action against many strains of Gram positive and Gram-negative organisms. The clavulanic acid component has little or no antimicrobial action. It does, however, by inactivation of susceptible beta-lactamase protect amoxicillin from degradation by beta-lactamase enzymes produced by penicillin resistant strains of organisms.
Clavulanic acid is an irreversible inhibitor of beta-lactamases produced by Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and Proteus vulgaris, H. influenzae, N. gonorrhoeae and B. fragilis (In-vitro activity does not necessarily imply in-vivo efficacy). Potassium clavulanate does not inactivate the chromosomally mediated (Sykes Type 1 Cephalosporinase) beta-lactamases produced by Acinetobacter species, Citrobacter species, Enterobacter, indole positive Proteus, Providencia species and Serratia marcescens.
Pharmacokinetics:
Absorption: The pharmacokinetic results for studies in which amoxicillin/clavulanic acid was administered to groups of healthy volunteers as either 500 mg/100 mg or 1000 mg/200 mg given as a bolus intravenous injection are presented below.

Mean (±SD) pharmacokinetic parameters *Bolus intravenous injection*					
Dose administered	Amoxicillin				
	Dose	Mean peak serum conc (µg/ml)	T 1/2 (h)	AUC (h.mg/l)	Urinary recovery (%, 0 to 6 h)
AMX/CA 500 mg/100 mg	500 mg	32.2	1.07	25.5	66.5
AMX/CA 1000 mg/200 mg	1000 mg	105.4	0.9	76.3	77.4
	Clavulanic acid				
AMX/CA 500 mg/100 mg	100 mg	10.5	1.12	9.2	46.0
AMX/CA 1000 mg/200 mg	200 mg	28.5	0.9	27.9	63.8
AMX – amoxicillin, CA – clavulanic acid					

Distribution: About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.
Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.
Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk.
Biotransformation: Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man, and eliminated in urine and faeces and as carbon dioxide in expired air.
Elimination: The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.
Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of a single 500/100 mg or a single 1000/200 mg bolus intravenous injection. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.
Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.
Age: The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.
Renal impairment: The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid.
Hepatic impairment: Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

Indication:

Clavospey is indicated for the treatment of infections caused by all organisms sensitive to amoxicillin, as well as those organisms which produce beta-lactamases that are sensitive to clavulanic acid. This includes:
- Acute bacterial sinusitis (adequately diagnosed);
- Acute otitis media;
- Acute exacerbations of chronic bronchitis (adequately diagnosed);
- Community acquired pneumonia;
- Cystitis;
- Pyelonephritis;
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis;
- Bone and joint infections, in particular osteomyelitis.

Recommended Dose and Mode of Administration:
Doses are expressed throughout in terms of Clavospey acid content except when doses are stated in terms of an individual component.
The dose of Clavospey that is selected to treat an individual infection should take into account:
The expected pathogens and their likely susceptibility to antibacterial agents.
The severity and the site of the infection.
The age, weight and renal function of the patient as shown below.
The use of alternative presentations of Clavospey (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.
The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review.
Consideration should be given to local guidelines on appropriate dosing frequencies for amoxicillin/clavulanic acid.
Adults and children ⩾ 40kg:
For treatment of infections as indicated in section **Indication**: 1g/ 0.2 g every 8 hours.
For surgical prophylaxis: For procedures less than 1 hour in duration, the recommended dose of Clavospey is 1g/0.2 g to 2g/0.2g given at induction of anaesthesia.
For procedures greater than 1 hour in duration, the recommended dose of Clavospey is 1g/0.2g to 2g/0.2g given at induction of anesthesia, with up to 3 doses of 1g/0.2g in 24 hours.
Clear clinical signs of infection at operation will require a normal course of intravenous or oral therapy post-operatively.
Children < 40 kg:
Recommended doses:
Children aged 3 months and over: 25 mg/5 mg per kg every 8 hours
Children aged less than 3 months or weighing less than 4 kg: 25 mg/5 mg per kg every 12 hours.
Elderly:
No dose adjustment is considered necessary.
Renal impairment:
Dose adjustments are based on the maximum recommended level of amoxicillin.
No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.
Adults and children ⩾ 40kg
CrCl: 10-30 ml/min: Initial dose of 1000 mg/200 mg and then 500 mg/100 mg given twice daily
CrCl < 10 ml /min: Initial dose of 1000 mg/200 mg and then 500 mg/100 mg given every 24 hours
Haemodialysis: Initial dose of 1000 mg/200 mg and then followed by 500 mg/100 mg every 24 hours, plus a dose of 500 mg/100 mg at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)
Children < 40 kg:
CrCl: 10 to 30 ml/min: 25 mg/5 mg per kg given every 12 hours
CrCl < 10 ml /min: 25 mg/5 mg per kg given every 24 hours
Haemodialysis: 25 mg/5 mg per kg given every 24 hours, plus a dose of 12.5 mg/2.5 mg per kg at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased).
Hepatic impairment:
Dose with caution and monitor hepatic function at regular intervals.
Method of administration:
Clavospey is for intravenous use.
Clavospey may be administered either by slow intravenous injection over a period of 3 to 4 min directly into a vein or via a drip tube or by infusion over 30 to 40 min. Clavospey is not suitable for intramuscular administration.
Children aged less than 3 months should be administered Clavospey by infusion only.
Treatment with Clavospey may be initiated by the use of an intravenous preparation and completed with an appropriate oral presentation as considered appropriate for the individual patient.

Contraindications:
- Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients;
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent;
- History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

Warnings and Precautions:
Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other beta-lactam agents.
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. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy should be discontinued and appropriate alternative therapy instituted.
In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.
This presentation of Clavospey may not be suitable for use when there is a high risk that the presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. As no specific data for T>MIC are available and the data for comparable oral presentations are borderline, this presentation (without additional amoxicillin) may not be suitable for the treatment of penicillin-resistant S. pneumoniae.
Convulsions may occur in patients with impaired renal function or in those receiving high doses.
Clavospey should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.
Prolonged use may occasionally result in overgrowth of non-susceptible organisms.
The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP). This reaction requires Clavospey discontinuation and contra-indicates any subsequent administration of amoxicillin.
Clavospey should be used with caution in patients with evidence of hepatic impairment.
Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.
Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, Clavospey should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation.
Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.
Prolongation of prothrombin time has been reported rarely in patients receiving Clavospey. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.
In patients with renal impairment, the dose should be adjusted according to the degree of impairment.
In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During administration of high doses of amoxicillin it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained.
During treatment with amoxicillin, 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.
The presence of clavulanic acid in Clavospey may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

Interactions with Other medicaments:
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.
Methotrexate: Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.
Probenecid: Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Pregnancy and Lactation:
During the I trimester should be administered with caution. Administration in the II and III trimester of pregnancy is considered safe. Amoxicillin is excreted in human milk but the excretion of clavulanic acid has not been studied conclusively therefore caution should be exercised when it is administered to nursing mothers.

Undesirable Effects:
The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea, and vomiting.
The ADRs derived from clinical studies and post-marketing surveillance with Clavospey, sorted by MedDRA System Organ Class are listed below.
Allergic skin reaction: urticaria, exanthem; erythematous circinate rash, rarely - erythema multiforme, extremely rare - exfoliative dermatitis, malignant exudative erythema multiforme (Stevens - Johnson), erythema multiforme.
Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain; abnormal liver function, elevated liver transaminases, in rare cases - pseudomembranous colitis;
Blood and lymphatic system: rarely - changes in the blood composition (leucopenia, thrombocytopenia, hemolytic anemia), prolonged prothrombin time (reversible);
Hepatobiliary system: rarely - cholestatic jaundice, hepatitis;
Immune system: rarely - angioedema, vasculitis;
Urinary system: interstitial nephritis, crystalluria;
Other: candidiasis, development of super infection. In rare cases - anaphylactic shock.

Overdose and Treatment:
Symptoms: Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed.
Convulsions may occur in patients with impaired renal function or in those receiving high doses.
Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained.
Treatment: Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

Dosage Forms and Packaging Available
1x1, 20 ml vial in a monocarton, with instruction for use.
Storage:
Keep in dry place protected from light at a temperature below 30°C. Keep out of reach of children.

Shelf life:
2 years. Do not use after expiry date.
The reconstituted solution should used immediately after preperation.

Distribution Condition:
Prescription only medicine (POM).