Public Assessment Report

Decentralised Procedure

MISKA
875 mg/125 mg Film-Coated Tablet

Applicant:
CRINOS S.p.A

Italian Marketing Authorisation Number: 043174

European procedure number: IT/H/0326/02/DC

TABLE OF CONTENTS

Module 1: Information about the initial procedure Page 3

Module 2: Summary of Product Characteristics Page 4

Module 3: Package Leaflets Page 20

Module 4: Labelling Page 27

Module 5: Scientific discussion during the initial procedure Page 30

I Introduction Page 30

II About the product Page 31

III Scientific Overview and discussion Page 32

III.1 Quality aspects Page 32

III.2 Non-clinical aspects Page 35

III.3 Clinical aspects Page 35

IV Overall conclusions and benefit-risk assessment Page 38

Module 1

Information about the Initial Procedure

Product Name	MISKA
Type of application	Article 10.1 of Directive 2001/83/EC as amended LINE EXTENSION
Active Substance	AMOXICILLIN TRIHYDRATE POTASSIUM CLAVULANATE
Form	FILM-COATED TABLETS
Strength	875 mg / 125 mg
MA Holder	CRINOS SPA VIA PAVIA 6 20136 MILAN ITALY
Reference Member State (RMS)	IT
Concerned Memember States (CMS)	NONE
Procedure number	IT/H/0326/002/DC
Timetable	End of procedure: Day 157 – 11 August 2016

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Italian version of the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.
Here is reported the English version of the SMPC approved at European level.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MISKA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Oval, white to crème-tinged film-coated tablets, scored on both sides.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Invented name] is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):
- 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.

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

4.2 Posology and method of administration

Posology

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of [invented name] that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- 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 [Invented name] (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For adults and children ≥ 40 kg, this formulation of [invented name] provides a total daily dose of 1750 mg amoxicillin/ 250 mg clavulanic acid with twice daily dosing and 2625 mg amoxicillin/375 mg clavulanic acid with three times daily dosing, when administered as recommended below.

For children < 40 kg, using other formulations of amoxicillin/clavulanic acid, a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, can be provided, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that adequate preparations of amoxicillin/clavulanic acid are selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

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 (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg

Recommended doses:

- standard dose: (for all indications) 875 mg/125 mg two times a day;
- higher dose - (particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 875 mg/125 mg three times a day.

Children < 40 kg

Children may be treated with amoxicillin/clavulanic acid tablets, suspensions or paediatric sachets.

Recommended doses:

- 25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given as two divided doses;
- up to 70 mg/10 mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

As the tablets cannot be divided children weighing less than 25 kg must not be treated with MISKA 875 mg/125 mg film-coated tablet

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 875 mg/125 mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above)
Amoxicillin [mg/kg body weight] per single dose (1 film-coated tablet)	21.9	25.0	29.2	35.0	12.5 – 22.5 (up to 35)
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.8 – 3.2 (up to 5)

Children weighing less than 25 kg should preferably be treated with amoxicillin/clavulanic acid suspension or paediatric sachets.

No clinical data are available for amoxicillin/clavulanic acid 7:1 formulations regarding doses higher than 45 mg/6.4 mg per kg per day in children under 2 years.

There are no clinical data for amoxicillin/clavulanic acid 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Elderly

No dose adjustment is considered necessary.

Renal impairment

No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

In patients with creatinine clearance less than 30 ml/min, the use of amoxicillin/clavulanic acid presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration

[Invented name] is for oral use.

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

Therapy can be started parenterally according to the SmPC of the IV-formulation and continued with an oral preparation.

Adults and children ≥ 40 kg

Recommended doses:

- standard dose: (for all indications) 875 mg/125 mg two times a day;
- higher dose - (particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 875 mg/125 mg three times a day.

Children < 40 kg

Children may be treated with amoxicillin/clavulanic acid tablets, suspensions or paediatric sachets.

Recommended doses:

- 25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given as two divided doses;
- up to 70 mg/10 mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

As the tablets cannot be divided children weighing less than 25 kg must not be treated with MISKA 875 mg/125 mg film-coated tablet

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins 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).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use

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

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 must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organism(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of amoxicillin/clavulanic acid is not 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. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid 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) (see section 4.8). This reaction requires amoxicillin/clavulanic acid discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

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 (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). 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, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal product 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 amoxicillin/clavulanic acid. 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 (see section 4.5 and 4.8).

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

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the 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 (see section 4.9).

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 amoxicillin/clavulanic acid may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

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 (see sections 4.4 and 4.8).

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.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.
Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breastfeeding

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

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

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin/clavulanic acid, 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: cannot be estimated from the available data

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Aseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	

Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders [7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

1 See section 4.4
2 See section 4.4
3 Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid at the start of a meal.
4 Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
5 A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
6 These events have been noted with other penicillins and cephalosporins (see section 4.4).
7 If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
8 See section 4.9
9 See section 4.4
10 See sections 4.3 and 4.4

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs of overdose

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 (see section 4.4).

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 (see section 4.4)

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility Breakpoints (µg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae[1]	≤ 1	-	> 1
Moraxella catarrhalis[1]	≤ 1	-	> 1
Staphylococcus aureus [2]	≤ 2	-	> 2
Coagulase-negative staphylococci [2]	≤ 0.25		> 0.25
Enterococcus[1]	≤ 4	8	> 8
Streptococcus A, B, C, G[5]	≤ 0.25	-	> 0.25
Streptococcus pneumoniae[3]	≤ 0.5	1-2	> 2
Enterobacteriaceae[1,4]	-	-	> 8
Gram-negative Anaerobes[1]	≤ 4	8	> 8
Gram-positive Anaerobes[1]	≤ 4	8	> 8
Non-species related breakpoints[1]	≤ 2	4-8	> 8

[1] The reported values are for amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l.
[2] The reported values are oxacillin concentrations.
[3] Breakpoint values in the table are based on ampicillin breakpoints.
[4] The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.
[5] Breakpoint values in the table are based on benzylpenicillin breakpoints.

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 infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Enterococcus faecalis
Gardnerella vaginalis
Staphylococcus aureus (methicillin-susceptible) [£]
*Coagulase-negative staphylococci (*methicillin-susceptible*)*
Streptococcus agalactiae
Streptococcus pneumoniae[1]
Streptococcus pyogenes and other beta-haemolytic streptococci
Streptococcus viridans group
Aerobic Gram-negative micro-organisms
Capnocytophaga spp.
Eikenella corrodens
Haemophilus influenzae[2]
Moraxella catarrhalis
Pasteurella multocida

Anaerobic micro-organisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella* spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecium* $ Aerobic Gram-negative micro-organisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia*
Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. [£] All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1] *Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each

case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (875 mg/125 mg tablets given twice daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0-24h)}$ (µg.h/ml)	$T_{1/2}$ (h)
Amoxicillin					
AMX/CA 875 mg/125 mg	875	11.64 ± 2.78	1.50 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21
Clavulanic acid					
AMX/CA 875 mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 0.12
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

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.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

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 dose of amoxicillin/clavulanic acid 250 mg/125 mg or 500 mg/125 mg tablets. 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 (see section 4.5).

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.

Gender

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

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 (see section 4.2).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate

gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Silica, colloidal anhydrous
Magnesium stearate
Talc
Povidone K25
Cellulose, microcrystalline
Crospovidone

Tablet film-coat
Triethyl citrate
Hypromellose
Talc
Titanium dioxide
Ethylcellulose
Cetyl alcohol
Sodium lauryl sulphate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium blisters (Alu/alu blisters) consisting of an aluminium forming foil with PVC coating on the inner side and of an aluminium lid foil, optionally printed (aluminium 25 µm, hard foil with a thermoplastic lacquer based on PVC on the inner side).

Package size: 12 film-coated tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<[To be completed nationally]>

Module 3

Package Leaflets

In accordance with Directive 2010/84/EU, the Italian version of the package leaflet for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.
Here is reported the English version of the PIL approved at European level.

Package leaflet: Information for the patient

MISKA 875 mg/125 mg film-coated tablet

Amoxicillin/clavulanic acid

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you (or for your child) only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What [invented name] is and what it is used for
2. What you need to know before you take [invented name]
3. How to take [invented name]
4. Possible side effects
5. How to store [invented name]
6. Contents of the pack and other information

1. What [invented name] is and what it is used for

[Invented name] is an antibiotic and works by killing bacteria that cause infections. It contains two different medicines called amoxicillin and clavulanic acid. Amoxicillin belongs to a group of medicines called “penicillins” that can sometimes be stopped from working (made inactive). The other active component (clavulanic acid) stops this from happening.

[Invented name] is used in adults and children to treat the following infections:

- middle ear and sinus infections
- respiratory tract infections
- urinary tract infections
- skin and soft tissue infections including dental infections
- bone and joint infections.

2. What you need to know before you take [invented name]

DO NOT take [invented name]:
- if you are allergic to amoxicillin, clavulanic acid, penicillin or any of the other ingredients of this medicine (listed in section 6)
- if you have ever had a severe allergic (hypersensitive) reaction to any other antibiotic. This can include a skin rash or swelling of the face or neck
- if you have ever had liver problems or jaundice (yellowing of the skin) when taking an antibiotic.

► **DO NOT take [invented name] if any of the above apply to you.** If you are not sure, talk to your doctor or pharmacist before taking [invented name].

Warnings and precautions
Talk to your doctor or pharmacist before taking this medicine if you:
- have glandular fever
- are being treated for liver or kidney problems
- are not passing water regularly.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking [invented name].

In some cases, your doctor may investigate the type of bacteria that is causing your infection. Depending on the results, you may be given a different strength of [invented name] or a different medicine.

Conditions you need to look out for
[Invented name] can make some existing conditions worse, or cause serious side effects. These include allergic reactions, convulsions (fits) and inflammation of the large intestine. You must look out for certain symptoms while you are taking [invented name], to reduce the risk of any problems. See *'Conditions you need to look out for'* in Section 4.

Blood and urine tests
If you are having blood tests (such as red blood cell status tests or liver function tests) or urine tests (for glucose), let the doctor or nurse know that you are taking [invented name]. This is because [invented name] can affect the results of these types of tests.

Other medicines and [invented name]
Tell your doctor or pharmacist if you are taking, have recently used or might use any other medicines.

If you are taking allopurinol (used for gout) with [invented name], it may be more likely that you will have an allergic skin reaction.

If you are taking probenecid (used for gout), your doctor may decide to adjust your dose of [invented name].

If medicines to help stop blood clots (such as warfarin) are taken with [invented name] then extra blood tests may be needed.

[Invented name] can affect how methotrexate (a medicine used to treat cancer or rheumatic diseases) works.

[Invented name] may affect how mycophenolate mofetil (a medicine used to prevent the rejection of transplanted organs) works.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
[Invented name] can have side effects and the symptoms may make you unfit to drive.
Do not drive or operate machinery unless you are feeling well.

3. How to take [invented name]

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults and children weighing 40 kg and over
- Usual dose - 1 tablet two times a day
- Higher dose - 1 tablet three times a day

Children weighing less than 40 kg
Children aged 6 years or less should preferably be treated with amoxicillin/clavulanic acid oral suspension or sachets.Ask your doctor or pharmacist for advice when giving this medicine to children weighing less than 40 kg. The tablets are not suitable for children weighing less than 25 kg.

Patients with kidney and liver problems
- If you have kidney problems the dose might be changed. A different strength or a different medicine may be chosen by your doctor.
- If you have liver problems you may have more frequent blood tests to check how your liver is working.

How to take [invented name]
- Swallow the tablets with a glass of water at the start of a meal or slightly before. Tablets can be broken along the score line to make them easier to swallow. You must take both pieces of the tablet at the same time.
- Space the doses evenly during the day, at least 4 hours apart. Do not take 2 doses in 1 hour.
- Do not take [invented name] for more than 2 weeks. If you still feel unwell you should go back to see the doctor.

If you take more [invented name] than you should
If you take too much [invented name], signs might include an upset stomach (feeling sick, being sick or diarrhoea) or convulsions. Talk to your doctor as soon as possible. Take the medicine carton to show the doctor.

If you forget to take [invented name]
If you forget to take a dose, take it as soon as you remember. You should not take the next dose to soon, but wait about 4 hours before taking the next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking [invented name]
Keep taking [invented name] until the treatment is finished, even if you feel better. You need every dose to help fight the infection. If some bacteria survive they can cause the infection to come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects below may happen with this medicine.

Conditions you need to look out for

Allergic reactions:
- skin rash
- inflammation of blood vessels *(vasculitis)* which may be visible as red or purple raised spots on the skin, but can affect other parts of the body
- fever, joint pain, swollen glands in the neck, armpit or groin
- swelling, sometimes of the face or mouth *(angioedema)*, causing difficulty in breathing
- collapse.

► **Contact a doctor immediately** if you get any of these symptoms. **Stop taking [invented name].**

Inflammation of large intestine
Inflammation of the large intestine, causing watery diarrhoea usually with blood and mucus, stomach pain and/or fever.

► **Contact your doctor as soon as possible** for advice if you get these symptoms.

Very common side effects (may affect more than 1 in 10 people)
- diarrhoea (in adults).

Common side effects (may affect up to 1 in 10 people)
- thrush (*candida* - a yeast infection of the vagina, mouth or skin folds)
- feeling sick (nausea), especially when taking high doses
  → if affected take [invented name] before food

- vomiting
- diarrhoea (in children).

Uncommon side effects (may affect up to 1 in 100 people)
- skin rash, itching
- raised itchy rash (*hives*)
- indigestion
- dizziness
- headache.

Uncommon side effects that may show up in your blood tests:
- increase in some substances (enzymes) produced by the liver.

Rare side effects (may affect up to 1 in 1,000 people)
- skin rash, which may blister, and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge – *erythema multiforme*)

► if you notice any of these symptoms contact a doctor urgently.

Rare side effects that may show up in your blood tests:
- low number of cells involved in blood clotting
- low number of white blood cells

Frequency not known (frequency cannot be estimated from the available data)
- Allergic reactions (see above)
- Inflammation of the large intestine (see above)
- Inflammation of the protective membrane surrounding the brain (*aseptic meningitis*)
- Serious skin reactions:
  - a widespread rash with blisters and peeling skin, particularly around the mouth, nose eyes and genitals *(Stevens- Johnson syndrome)*, and a more severe form, causing extensive peeling of the skin (more than 30% of the body surface – *toxic epidermal necrolysis*)
  - widespread red skin rash with small pus-containing blisters (*bullous exfoliative dermatitis*)
  - a red, scaly rash with bumps under the skin and blisters (*exanthemous pustulosis*).

► **Contact a doctor immediately if you get any of these symptoms.**

- inflammation of the liver (*hepatitis*)
- jaundice, caused by increases in the blood of bilirubin (a substance produced in the liver) which may make your skin and whites of the eyes appear yellow
- inflammation of tubes in the kidney
- blood takes longer to clot
- hyperactivity
- convulsions (in people taking high doses of [invented name] or who have kidney problems)
- black tongue which looks hairy

Side effects that may show up in your blood or urine tests:
- severe reduction in the number of white blood cells
- low number of red blood cells (*haemolytic anaemia*)
- crystals in urine.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [invented name]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton.
The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Do not store above 30°C. Store in the original package in order to protect from moisture.

6. Contents of the pack and other information

What [invented name] contains

The active substances are amoxicillin trihydrate and potassium clavulanate.

Each film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

The other ingredients are:
Tablet core
Colloidal anhydrous silica, magnesium stearate, talc, povidone K25, microcrystalline cellulose, crospovidone

Tablet film-coat
Triethyl citrate, hypromellose, talc, titanium dioxide, ethylcellulose, cetyl alcohol, sodium lauryl sulphate

What [invented name] looks like and contents of the pack

[Invented name] are oval, white to crème-tinged film-coated tablets, scored on both sides.
The score line is only there to help you break the tablet if you have difficulty swallowing it whole.

Aluminium blisters (Alu/alu blisters) consisting of an aluminium forming foil with PVC coating on the inner side and of an aluminium lid foil, optionally printed (aluminium 25 µm, hard foil with a thermoplastic lacquer based on PVC on the inner side).

Package size: 12 film-coated tablets.

Marketing Authorisation Holder and Manufacturer
[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[To be completed nationally]

This leaflet was last revised in <{MM/YYYY}>

[To be completed nationally]

Advice/medical education

Antibiotics are used to treat infections caused by bacteria. They have no effect against infections caused by viruses.

Sometimes an infection caused by bacteria does not respond to a course of an antibiotic. One of the commonest reasons for this to occur is because the bacteria causing the infection are resistant to the antibiotic that is being taken. This means that they can survive and even multiply despite the antibiotic.

Bacteria can become resistant to antibiotics for many reasons. Using antibiotics carefully can help to reduce the chance of bacteria becoming resistant to them.

When your doctor prescribes a course of an antibiotic it is intended to treat only your current illness. Paying attention to the following advice will help prevent the emergence of resistant bacteria that could stop the antibiotic working.

1. It is very important that you take the antibiotic at the right dose, at the right times and for the right number of days. Read the instructions on the label and if you do not understand anything ask your doctor or pharmacist to explain.
2. You should not take an antibiotic unless it has been prescribed specifically for you and you should use it only to treat the infection for which it was prescribed.
3. You should not take antibiotics that have been prescribed for other people even if they had an infection that was similar to yours.
4. You should not give antibiotics that were prescribed for you to other people.
5. If you have any antibiotic left over when you have taken the course as directed by your doctor you should take the remainder to a pharmacy for appropriate disposal.

Module 4

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 875 mg/125 mg film-coated tablet

Amoxicillin/clavulanic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {mm/yyyy}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

{BLISTER}

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 875 mg/125 mg film-coated tablet

Amoxicillin/clavulanic acid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

Module 5

Scientific discussion during the initial procedure

I. Introduction

Based on the review of the data and the Applicant's response to the questions raised by RMS on quality, safety and efficacy, the RMS considers that the applications MISKA 875 mg/125 mg Film-Coated Tablets (MA No 042174; Procedure No IT/H/0326/002/DC) is approvable.
This product is a prescription-only medicine indicated for the treatment of:

- 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.

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.

This is a Decentralised application submitted under Article 10(1) of Directive 2001/83/EC, as line extension of the existing marketing authorisation for MISKA 875 mg + 125 mg Granulate for oral suspension.
The originator product is Augmentin 875 mg/125 mg Film- Coated Tablets by GlaxoSmithKline Pharma GmbH, registered since 04.04.1996.
The Applicant demonstrates the essential similarity between test and reference product and in support of this procedure a report on bioequivalence study has been submitted (Project Nr. 120043).

MISKA is a medicine consisting of a combination of two active substances: amoxicillin and clavulanic acid (ATC code: J01CR02).
Mechanism of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.
Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

The Applicant demonstrates the essential similarity between test and reference product and in support of this procedure a report on bioequivalence study has been submitted. Compliance to GCP/GLP was stated.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. A declaration by the QP at the site responsible for batch release that the active substances are manufactured in accordance with the detailed Guidelines on GMP for starting materials was submitted.

II. About the product

Proposed name of the medicinal product in the RMS	MISKA
Name of the drug substances (INN name):	Amoxicillin trihydrate and Potassium clavulanate
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.
Pharmaceutical form(s) and strength(s):	Film-coated tablets, 875 mg/125 mg
Reference Number(s) for the Decentralised Procedure	IT/H/0326/002/DC
Reference Member State:	IT
ConcernedMemberStates:	none
Marketing Authorisation Numbers	AIC No: 042174
Name and address of the Authorization Holder	CRINOS SPA VIA PAVIA 6 20136 MILAN ITALY

III. Scientific Overview and discussion

III.1 Quality aspects

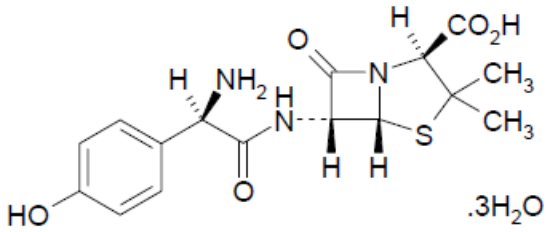
ACTIVE SUBSTANCE – amoxicillin trihydrate

INN name: Amoxicillin

Chemical name (IUPAC): (2S,5R,6R)-6-[R-(-)-2-amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

CAS Reg. No.: 61336-70-7

Structural formula



Molecular formula: $C_{16}H_{19}N_3O_5S \cdot 3H_2O$

Relative Molecular mass: 419.5 (trihydrate form) // 365.4 (anhydrous)

Physical form: white or almost white crystalline powder

Solubility: slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides

The active substance is described in the relevant monograph of the European Pharmacopeia.
All aspects of the manufacture and control of the active substance amoxicillin trihydrate, except for the proposed packaging specifications and stability data are covered by a Certificate of Suitability issued by EDQM.
Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

ACTIVE SUBSTANCE – Potassium Clavulanate

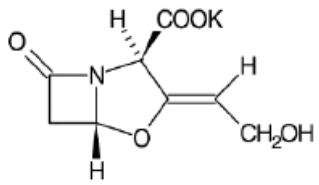
INN name: clavulanic acid (this refers to the Potassium salt of Clavulanic acid)

Chemical name (IUPAC): (Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-

1-azabicyclo[3.2.0]heptane-2-carboxylate

CAS Reg. No.: 61177-45-5

Structural formula:



Molecular formula: $C_8H_8NO_5K$

Relative Molecular mass: 237.3 (as the Potassium salt) // 199.2 (as the free acid)

Physical form: white or almost white crystalline powder

Solubility: Freely soluble in water, slightly soluble in ethanol (96 per cent), very slightly soluble in acetone.

The active substance is described in the relevant monograph of the European Pharmacopeia.
All aspects of the manufacture and control of the active substance potassium clavulanate, except for the proposed packaging specifications and stability data are covered by a Certificate of Suitability issued by EDQM.
Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

The applied product 825 mg/125 mg film-coated tablets were developed as immediate release tablets for oral administration.The medicinal product is presented as oval, white to crème-tinged tablets, scored on both sides. The size is approx. 10.5 x 22.5 mm.

Other Ingredients
Other ingredients are:
Tablet core
Silica, colloidal anhydrous, Magnesium stearate, Talc, Povidone K25, Cellulose, microcrystalline, Crospovidone
Tablet film-coat
Triethyl citrate, Hypromellose, Talc, Titanium dioxide, Ethylcellulose, Cetyl alcohol, Sodium lauryl sulphate

All the excipients comply with their respective European Pharmacopeia monographs.
Magnesium stearate is of vegetable origin to eliminate a potential BSE/TSE risk.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.
There are no excipients of human or animal origin.

Pharmaceutical Development

The formulation of MISKA 875 mg/ 125 mg film-coated tablets has been developed based on the formulation of the already authorized European brand leader product Augmentin 1g film-coated tablets manufactured and distributed by GSK.
Each amoxicillin clavulanic acid film-coated tablet contains 875 mg of amoxicillin in the form of amoxicillin trihydrate and 125 mg of clavulanic acid in the form of potassium clavulanate.
Suitable pharmaceutical development data have been provided for this application.
Dissolution profiles of the Sandoz and the originator batches used in the BE study are presented in four different media. Results demonstrate that Sandoz´s product shows a dissolution behavior comparable to the innovator´s product based on calculation of the similarity factor f2.
The film-coated tablets are packaged in aluminium blisters.

Manufacturing Process

The product is manufactured by conventional standard procedures for film-coated tablets: sieving, mixing, screening, tableting, film-coating, drying and filling.
Satisfactory batch formula has been provided for the manufacture of the medicinal product, along with an appropriate description of the manufacturing process. The manufacturing process has been validatedon three industrial batches.

Control of Finished Product

The finished product specifications are satisfactory: parameters and limits are considered adequate to control the quality of the drug product. Test methods have been described and adequately validated, as appropriate.
Batch data have been provided and comply with the release specifications.
Certificates of Analysis have been also provided.

Container Closure System
The film-coated tablets are packaged in Aluminium blisters (Alu/Alu blister) consisting of an Aluminium forming foil with PVC coating on the inner side and of an Aluminium lid foil, optionally printed (Aluminium 25µm, hard foil with a thermoplastic lacquer based on PVC on the inner side).
adequate documentations on the container closure system for the finished product have been provided.
Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European Regulations concerning materials in contact with foodstuff .

Pack size: 12 tablets.

Stability
Finished product stability studies were performed according to the current ICH stability Guidelines on batches of finished product in the final proposed packaging. Based on results, a shelf life of 2 years has been justify when the product is stored in the original package, in order to protect it from moisture and at temperature not above 30°C.
A photostability study was carried out according to the relevant guideline demonstrating that the drug product can be considered as not being light sensitive.
Bulk stability study results (6 months) of one batch of film-coated tablets packaged in the applied bulk container PETP-Alu-PETP-PE bag supported a bulk stability of 6 months at 25°C/60%RH.

III.2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Amoxicillin Trihydrate and Clavulanic Acid are well known. As Amoxicillin Trihydrate and Clavulanic Acid are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is deemed appropriate.

Ecotoxicity/environmental risk assessment (ERA)

Since MISKA is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

To support the application, the applicant has submitted as report one bioequivalence study (Project Nr. 120043): RANDOMISED, OPEN-LABEL, 3-WAY REFERENCE-REPLICATED, CROSSOVER, BIOEQUIVALENCE STUDY OF AMOXICILLIN-CLAVULANIC ACID 875 mg-125 mg TABLET AND AUGMENTIN (REFERENCE) FOLLOWING A 875 mg-125 mg DOSE IN HEALTHY SUBJECTS AT THE

BEGINNING OF A HIGH FAT BREAKFAST. The study was conducted in the centre PharmaNet Canada, Inc.
Test and reference compared during the study was the following:
A) Amoksiklav® (amoxicillin - clavulanic acid), manufactured by SANDOZ GmbH, Austria (batch number CJ8631)
B) Augmentin® (amoxicillinclavulanic acid) manufactured by SmithKlineBeecham Pharmaceuticals, Great Britain, (batch number 562800).
This study met the bioequivalence criteria as all 90% geometric confidence intervals were within the acceptance range. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

This was a single centre, randomised, single-dose, open-label, 3-way, reference replicated crossover BE study to compare the rate and extent of absorption of a test amoxicillin-clavulanic acid versus Augmentin, a reference amoxicillin-clavulanic acid, at the beginning of a high-fat, high calorie meal. A total of 51 healthy adult subjects were included in this study. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomisation scheme generated by PharmaNet. Subjects were confined to the PharmaNet Clinical Facility from at least 10 hours prior to drug administration until after the 10.0-hour post-dose blood draw, in each period. The treatment phases were separated by washout periods of 7 days.
The study, both clinical and analytical part, were conducted at PharmaNet Canada Inc., 2500, rue Einstein, Québec (Québec), Canada, G1P 0A2. The Study Period was:
First dosing: 2012-10-19
Study exit procedures: 2012-11-02
Subjects were served a high-fat, high-calorie breakfast (meal content was in accordance with the EMA [CPMP/QWP/EWP/1401/98 Rev.1]).
Blood samples were collected prior to study drug administration and 0.250, 0.500, 0.750, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 4.00, 5.00, 6.00, 8.00, and 10.0 hours post-dose, in each period. All blood samples were drawn into blood collection tubes (3 mL) containing K_3-EDTA.

Pharmacokinetic Variables
The following pharmacokinetic parameters will be calculated by standard non-compartmental methods for amoxicillin and clavulanic acid:
1) AUC0-t: area under the concentration-time curve from time zero to the last non-zero concentration
2) AUC0-inf: area under the concentration-time curve from time zero to infinity (extrapolated)
3) Cmax: maximum observed concentration
4) Residual area: calculated as 100*(1- AUC0-t / AUC0-inf)
5) Tmax: time of observed Cmax
6) T½ el: elimination half-life
7) Kel: elimination rate constant

Criteria for bioequivalence for amoxicillin and clavulanic acid:
• For amoxicillin, 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC0-t and Cmax should be within 80.00% to 125.00%.

• For clavulanic acid, the 90% geometric confidence interval of the ratio (T/R) of least-squares means of the test to reference product of ln-transformed AUC0-t should be within 80.00% to 125.00%.

Results

Amoxicillin

Table 11.4.2.3-3: Ratios, 90% geometric confidence intervals, intra- and inter-subject CVs for AUC_{0-t}, AUC_{0-inf}, and C_{max} for amoxicillin

			90% Geometric C.I.[2]			
Parameter	Treatment Comparisons	Ratio[1]	Lower	Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	Test(A) - Reference(B)	97.10%	90.04%	104.70%	15.90%	21.94%
AUC_{0-inf}	Test(A) - Reference(B)	97.22%	90.20%	104.80%	15.81%	22.28%
C_{max}	Test(A) - Reference(B)	96.10%	88.09%	104.83%	18.37%	25.24%

[1] Calculated using least-squares means according to the formula: $e^{(A-B)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Clavulanic Acid

Table 11.4.2.3-6: Ratios, 90% geometric confidence intervals and intra-subject CVs for the reference for AUC_{0-t}, AUC_{0-inf}, and C_{max} for clavulanic acid

			90% Geometric C.I.[2]		
Parameter	Treatment Comparisons	Ratio[1]	Lower	Upper	Intra-Subject CV for Reference
AUC_{0-t}	Test(A) - Reference(B)	102.50%	97.53%	107.73%	19.93%
AUC_{0-inf}	Test(A) - Reference(B)	102.51%	97.64%	107.64%	19.45%
C_{max}	Test(A) - Reference(B)	101.81%	95.38%	108.68%	25.59%

[1] Calculated using least-squares means according to the formula: $e^{(A-B)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.

Clinical efficacy

The efficacy of Amoxicillin and Clavulanic Acid is well-known. No new efficacy data have been submitted and none are required for applications of this type.

Clinical safety

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

A summary of Pharmacovigilance System has been presented. As described by the applicant, it fulfills the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Applicant has submitted a risk management plan (version 1.1, July 2016), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to amoxicillin and clavulanic acid.

SUMMARIES OF PRODUCT CHARACTERISTICS (Sm.PCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING

The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the originator products, where appropriate, along with current guidelines. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with current guidance.

The packed leaflet has been evaluated via user consultation study in accordance with the requirements of articles 59(3) and 61(1) of directive 2001/83/EC. The language used for the purpose of the user testing PIL was English.

IV Overall conclusions and benefit-risk assessment

The quality characteristics of MISKA “875mg + 125 mg Film-Coated Tablets” are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

The Applicant demonstrates the essential similarity between test and reference product and in support of this procedure a report on bioequivalence study has been submitted (Project Nr. 120043).

The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFITI RISK ASSESSMENT

The quality of the product MISKA is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Bioequivalence with the reference product has been demonstrated and no new or unexpected safety concerns have been raised during the bioequivalence study.

Therefore the benefit/risk balance is considered to be positive.