RISK MANAGEMENT PLAN (RMP) in the EU

Active substance(s) (INN or common name):	amoxicillin/clavulanic acid
Pharmaco-therapeutic group (ATC Code):	Combinations of penicillins, incl. beta-lactamase inhibitors; J01CR02.
Name of Marketing Authorisation Holder or Applicant:	Krka d.d., Novo mesto TAD Krka Sverige Krka Farma d.o.o
Product(s) concerned (brand name(s)):	Betaklav 500 mg /125 mg Betaklav 875 mg/ 125 mg Betaklav 457 mg/ 5 ml Amoxicillin/ Clavulansäure Krka 500 mg / 125 mg Filmtabletten Amoxicillin/ Clavulansäure Krka 875 mg / 125 mg Filmtabletten Бетаклав 500 mg + 125 mg филмирани таблетки (Betaklav 500 mg + 125 mg film coated tablets) Бетаклав 875 mg + 125 mg филмирани таблетки (Betaklav 875 mg + 125 mg film coated tablets) Бетаклав 457 mg/ 5 ml прах за перорална суспензия (Betaklav 457 mg/ 5 ml powder for oral suspension) Amoxicillin/ Clavulansäure TAD 500 mg/ 125 mg Filmtabletten Amoxicillin/ Clavulansäure TAD 875 mg/ 125 mg Filmtabletten Amoxicillin + clavulanic acid TAD 400 mg/5ml + 57 mg/5 ml Pulver zur Herstellung einer Suspension zum Einnehmen Amoxicilin / clavulanic acid Krka 500 mg / 125 mg film coated tablets Amoxicilin / clavulanic acid Krka 875 mg / 125 mg film coated tablets Betaklav Betaklav 500 mg + 125 mg filmtabletta Betaklav 875 mg + 125 mg filmtabletta Betaklav 457 mg/ 5 ml por belsőleges szuszpenzióhoz Betaklav 500 mg + 125 mg filmom obložene tablete Betaklav 875 mg + 125 mg filmom obložene tablete Betaklav 457 mg/ 5 ml prašak za oralnu

	suspenziju Amoxicilin / clavulanic acid Krka 500 mg / 125 mg film coated tablets Amoxicillina e acido clavulanico Krka Betaklav 500 mg / 125 mg plėvele dengtos tabletės Betaklav 875 mg / 125 mg plėvele dengtos tabletės Betaklav 457 mg/ 5 ml milteliai geriamajai suspensijai Betaklav 500 mg / 125 mg apvalkotās tabletes Betaklav 875 mg / 125 mg apvalkotās tabletes Betaklav 457 mg/ 5 ml pulveris iekšķīgi lietojamas suspensijas pagatavošanai Hiconcil combi Amoxicilina + Ácido clavulânico Krka 500 mg + 125 mg comprimidos revestidos por película Amoxicilina + Ácido clavulânico Krka 875 mg + 125 mg comprimidos revestidos por película Amoxicilina + Ácido clavulânico Krka 457 mg + 5 ml Pó para suspensão oral Amoxicillinum + acidum clavulanicum Krka 500 mg /125 mg comprimate filmate Amoxicillinum + acidum clavulanicum Krka 875 mg /125 mg comprimate filmate Amoxicillinum + acidum clavulanicum Krka 400 mg/ 57 mg/ 5 ml pulbere pentru suspensie orală Betaklav 500 mg / 125 mg filmom obalené tablety Betaklav 875 mg / 125 mg filmom obalené tablety Betaklav 457 mg/ 5 ml prášok na perorálnu suspenziu Betaklav 500 mg / 125 mg filmsko obložene tablete Betaklav 875 mg / 125 mg filmsko obložene tablete Betaklav 400 mg + 57 mg/ 5 ml prašek za peroralno suspenzijo

Data lock point for this RMP	3.6.2015	Version number	1.3
Date of final sign off	3.6.2015		

Planned update of RMP:

- At the request of regulatory authority;

1.8.2 clean	Amoxicillin trihydrate + Clavulanate potassium
Risk Management System	film-coated tablets

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Part	**Module/annex**	**Date last updated for submission (sign off date)**	***Version number of RMP when last submitted/ or Not Applicable**
PART II Safety Specification	SV Post-authorisation experience	NA	NA
	SVIII Summary of the safety concerns	22.4.2015	1.2
PART III Pharmacovigilance Plan		22.4.2015	1.2
PART IV Plan for post-authorisation efficacy studies		NA	NA
PART V Risk Minimisation Measures		3.6.2015	1.3
PART VI Summary of RMP		3.6.2015	1.3
PART VII Annexes	ANNEX 1 EudraVigilance	NA	NA
	ANNEX 2 Current or proposed SmPC/PIL	3.6.2015	1.3
	ANNEX 3 Worldwide marketing status by country	NA	NA
	ANNEX 4 Synopsis of clinical trial programme	NA	NA
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	NA	NA
	ANNEX 6 Protocols for proposed and on-going studies in Part III	NA	NA

	ANNEX 7 Specific adverse event follow-up forms	NA	NA
	ANNEX 8 Protocols for studies in Part IV	NA	NA
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	NA	NA
	ANNEX 10 Details of proposed additional risk minimisation activities	NA	NA
	ANNEX 11 Mock up examples	NA	NA
	ANNEX 12 Other supporting data	22.4.2015	1.2

Prepared by Anica Ranfl, MD……

Approved by Krka's QPPV: Irena Orel MD, MSc.....……

QPPV signature ……

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Overview of versions:

Version number of last agreed RMP:

Version number	Not applicable
Agreed within	Not applicable

Current RMP versions under evaluation:
This is the first RMP. No RMP versions are under evaluation.

Part I: Product(s) Overview

Invented name(s) in the European Economic Area (EEA)	Betaklav 500 mg /125 mg Betaklav 875 mg/ 125 mg Betaklav 457 mg/ 5 ml Amoxicillin/ Clavulansäure Krka 500 mg / 125 mg Filmtabletten Amoxicillin/ Clavulansäure Krka 875 mg / 125 mg Filmtabletten Бетаклав 500 mg + 125 mg филмирани таблетки (Betaklav 500 mg + 125 mg film coated tablets) Бетаклав 875 mg + 125 mg филмирани таблетки (Betaklav 875 mg + 125 mg film coated tablets) Бетаклав 457 mg/ 5 ml прах за перорална суспензия (Betaklav 457 mg/ 5 ml powder for oral suspension) Amoxicillin/ Clavulansäure TAD 500 mg/ 125 mg Filmtabletten Amoxicillin/ Clavulansäure TAD 875 mg/ 125 mg Filmtabletten Amoxicillin + clavulanic acid TAD 400 mg/5ml + 57 mg/5 ml Pulver zur Herstellung einer Suspension zum Einnehmen Amoxicilin / clavulanic acid Krka 500 mg / 125 mg film coated tablets Amoxicilin / clavulanic acid Krka 875 mg / 125 mg film coated tablets Betaklav Betaklav 500 mg + 125 mg filmtabletta Betaklav 875 mg + 125 mg filmtabletta Betaklav 457 mg/ 5 ml por belsőleges szuszpenzióhoz Betaklav 500 mg + 125 mg filmom obložene tablete Betaklav 875 mg + 125 mg filmom obložene tablete Betaklav 457 mg/ 5 ml prašak za oralnu suspenziju Amoxicilin / clavulanic acid Krka 500 mg / 125 mg film coated tablets Amoxicillina e acido clavulanico Krka Betaklav 500 mg / 125 mg plėvele dengtos tabletės Betaklav 875 mg / 125 mg plėvele dengtos tabletės Betaklav 457 mg/ 5 ml milteliai geriamajai suspensijai Betaklav 500 mg / 125 mg apvalkotās tabletes Betaklav 875 mg / 125 mg apvalkotās tabletes Betaklav 457 mg/ 5 ml pulveris iekšķīgi lietojamas suspensijas pagatavošanai Hiconcil combi Amoxicilina + Ácido clavulânico Krka 500 mg + 125 mg comprimidos revestidos por película Amoxicilina + Ácido clavulânico Krka 875 mg + 125 mg comprimidos revestidos por película Amoxicilina + Ácido clavulânico Krka 457 mg + 5 ml Pó para suspensão oral Amoxicillinum + acidum clavulanicum Krka 500 mg /125 mg comprimate filmate Amoxicillinum + acidum clavulanicum Krka 875 mg /125 mg

	comprimate filmate Amoxicillinum + acidum clavulanicum Krka 400 mg/ 57 mg/ 5 ml pulbere pentru suspensie orală Betaklav 500 mg / 125 mg filmom obalené tablety Betaklav 875 mg / 125 mg filmom obalené tablety Betaklav 457 mg/ 5 ml prášok na perorálnu suspenziu Betaklav 500 mg / 125 mg filmsko obložene tablete Betaklav 875 mg / 125 mg filmsko obložene tablete Betaklav 400 mg + 57 mg/ 5 ml prašek za peroralno suspenzijo
Authorisation procedure	**decentralised**
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	Amoxicillin is 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 time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.
Indication(s) in the EEA Current (if applicable)	Amoxicillin/clavulanic acid 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.
Proposed (if applicable)	Not applicable.
	Doses are expressed throughout in terms of

Posology and route of administration in the EEA Current (if applicable)	amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component. The dose of amoxicillin/clavulanic 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 amoxicillin/clavulanic (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 Amoxicillin/clavulanic acid 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, this formulation of Amoxicillin/clavulanic acid provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Amoxicillin/clavulanic acid is 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). ***Doses of amoxicillin/clavulanic acid 7:1 formulations:*** ***Betaklav 875 mg/ 125 mg*** ***Betaklav 457 mg/ 5 ml*** <u>Adults and children ≥ 40 kg</u> 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, or suspensions. 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). 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). ***Doses of amoxicillin/clavulanic acid 4:1 formulations:*** ***Betaklav 500 mg/125 mg film-coated tablets*** Adults and children ≥ 40 kg One 500 mg/125 mg tablet taken three times a day. Children < 40 kg 20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses. Children may be treated with amoxicillin/clavulanic acid tablets or suspensions. As the tablets cannot be divided children weighing less than 25 kg must not be treated with amoxicillinl/clavulanic tablets. Children aged 6 years and below should preferably be treated with amoxicillinl/clavulanic acid suspension. No clinical data are available on doses of amoxicillin/clavulanic acid 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years. Elderly No dose adjustment is considered necessary.

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin.

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

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily)
CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg)
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

Hepatic impairment

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

Method of administration

Amoxicillin/clavulanic acid 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.

	Shake the bottle before each dose (see section 6.6).
Proposed (if applicable)	Not applicable.
Pharmaceutical form(s) and strengths Current (if applicable)	500 mg/125 mg film-coated tablet, 875 mg/125 mg, 400 mg/57 mg/5 ml powder for oral suspension
Proposed (if applicable)	Not applicable.

Country and date of first authorization worldwide	NA	NA
Country and date of first launch worldwide	NA	NA
Country and date of first authorisation in the EEA	NA	NA

Is the product subject to additional monitoring in the EU? Yes ☐ No ☒

Part II: Module SV- Post-authorisation experience

Not applicable. This module is only required for updates to the RMP.

Part II: Module SVIII- Summary of the safety concerns

Important identified risks:	Antibiotic associated colitis
	Renal impairment and risk of convulsion
	Interaction with oral anticoagulants
	Patient with reduced urine output
	False positivity of laboratory findings
	Serious allergic skin reactions (including acute generalised exanthemous pustulosis - AGEP)
	Hypersensitivity reaction to any penicillins and history of sever immediate hypersensitivity reaction to another beta-lactam agent (cephalosporin, carbapenem, monobactam)
	Hepatic impairment and history of hepatic impairment due

	to amoxicillin/clavulanic acid
	Haematological ADRs (leucopenia, agranulocytosis)
	Occurrence of a morbilliform rash if Amoxicillin/clavulanic acid is used in infectious mononucleosis
Important potential risks:	Overgrowth of non-susceptible organisms and antibiotic resistance - prolonged use
	Concomitant use with allopurinol
	Concomitant use with methotrexate
	Concomitant use with probenecid
Missing information:	Use in pregnancy and lactation
	Dosage of 7:1 ration presentations in patients with renal impairment with creatinine clearance less than 30ml/min

Part III: Pharmacovigilance Plan

This part is only required if reference product has additional PhV activities. To our best knowledge we are not aware of any originator's additional PhV activities.

Part IV: Plans for post-authorisation efficacy studies

Not applicable. This module is only required if reference product has on-going or planned post-authorisation efficacy studies. To our best knowledge we are not aware of any originator's post-authorisation efficacy studies.
No post-authorisation efficacy studies are planned.

Part V: Risk minimisation measures

V.1 Risk minimisation measures by safety concern

Safety concern	**Antibiotic associated colitis**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient

	information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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, <Invented name> should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation. **Section 4.8**. Undesirable effects Listed as: Antibiotic-associated colitis (Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)) The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.

Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Renal impairment and risk of convulsions**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.2** Posology and method of Administration 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. **Section 4.4** Special warnings and precautions for use Convulsions may occur in patients with impaired renal function or in those receiving high doses **Section 4.8** Undesirable effects Listed as Convulsions **Section 4.9** Overdose Convulsions may occur in patients with impaired renal function or in those receiving high doses. The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).

Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Interaction with oral anticoagulants**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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). **Section 4.5** Interaction with other medicinal products and other forms of interaction 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). **Section 4.8** Undesirable effects Listed as Prolongation of bleeding time and

	prothrombin time The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Patients with reduced urine output**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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). **Section 4.8** Undesirable effects Listed as Crystalluria **Section 4.9** Overdose Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4). The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**False positivity of laboratory findings**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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 <Invented name> 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. The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).

Criteria for judging the success of the proposed risk minimisation measures	Decreased or the same frequency of case reports, with false positivity laboratory findings, comparing to the previous periods.The frequency of appearance of crystalluria in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Serious allergic skin reactions (including acute generalised exanthemous pustulosis - AGEP)**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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 <Invented name> discontinuation and contra-indicates any subsequent administration of amoxicillin. **Section 4.8** Undesirable effects Listed as Stevens-Johnson syndrome Toxic epidermal necrolysis Bullous exfoliative-dermatitis Acute generalised exanthemous pustulosis (AGEP) The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.

Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Hypersensitivity reaction to any penicillins and history of sever immediate hypersensitivity reaction to another beta-lactam agent (cephalosporin, carbapenem, monobactam)**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.3** Contraindications History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam). **Section 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). **Section 4.8** Undesirable effects Listed asAngioneurotic oedema, Anaphylaxis, Serum sickness-like syndrome, Hypersensitivity vasculitis The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Hepatic impairment and history of hepatic impairment due to amoxicillin/clavulanic acid**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals

	(proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.2** Posology and method of administration Patients with hepatic impairment Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4)**Section 4.3** Contraindications History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8). **Section 4.4** Special warnings and precautions for use 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). Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. **Section 4.8** Undesirable effects Listed as: Rises in AST and/or ALT5, Hepatitis, Cholestatic jaundice The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	

How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Haematological ADRs (leucopenia, agranulocytosis)**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. **Section 4.8** Undesirable effects Listed as: reversible leucopenia (including neutropenia), reversible agranulocytosis The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Occurrence of a morbilliform rash if Amoxicillin/clavulanic acid is used in infectious mononucleosis**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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. **Section 4.8** Undesirable effects Listed as rash. The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.

Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Overgrowth of non-susceptible organisms and antibiotic resistence – prolonged use**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use Prolonged use may occasionally result in overgrowth of non-susceptible organisms. **Section 4.8** Undesirable effects Listed as: Overgrowth of non-susceptible organisms The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.

Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The frequency of appearance of this adverse reaction and its consequences decreased or in the expected range.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Concomitant use with allopurinol**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.

Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	Decreased or the same frequency of case reports, with allopurinol used together with amoxicillin/clavulanic acid which resulted in the adverse events, comparing to the previous periods.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Concomitant use with methotrexate**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.5** Interaction with other medicinal products and other forms of interaction Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.

Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	Decreased or the same frequency of case reports, with methotrexate used together with amoxicillin/clavulanic acid which resulted in the adverse events, comparing to the previous periods.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Concomitant use with probenecid**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4.5** Interaction with other medicinal products and other forms of interaction 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. **Section 5.2** Pharmacokinetic properties Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

	The similar content is proposed also in corresponding sections of PIL. Comment (e.g. on any differences between SmPCs) Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	Decreased or the same frequency of case reports, with probenecid used together with amoxicillin/clavulanic acid which resulted in the adverse events, comparing to the previous periods.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Use in pregnancy and lactation**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 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. Brestfeeding 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. The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The appearance of case reports regarding use in pregnancy or during lactation.
Planned dates for assessment	At the time of PSUR or evaluation of safety

	profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

Safety concern	**Dosage of 7:1 ration presentations in patients with renal impairment with creatinine clearance less than 30 ml/min**
Objective(s) of the risk minimisation measures	Raising awareness of health professionals (proposed SmPC) and patients (patient information leaflet).
Routine risk minimisation measures	(Proposed) content in SPC **Section 4**.2 Posology and method of Administration No clinical data are available for <Invented name> 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 <Invented name> 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made. In patients with creatinine clearance less than 30 ml/min, the use of <Invented name> presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available. The similar content is proposed also in corresponding sections of PIL.
	Comment (e.g. on any differences between SmPCs)
	Prescription only medicine.
Additional risk minimisation measure(s) (repeat as necessary)	None proposed

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance- assessment of ICSR, PSUR and periodic benefit risk assessment during signal management procedure (cumulative and periodical (every year) review of all cases reported from any source in the regular PSUR and in the signal management procedure).
Criteria for judging the success of the proposed risk minimisation measures	The appearance of case reports with ADRs regarding use of 7:1 formulations in doses higher than 45 mg/6.4 mg per kg per day in children under 2 years. The appearance of case reports with ADRs regarding use of 7:1 formulations in children under 2 months of age. The appearance of case reports with ADRs regarding use of 7:1 ration presentations in patients with renal impairment with creatinine clearance less than 30 ml/min.
Planned dates for assessment	At the time of PSUR or evaluation of safety profile during signal management procedure.
Results of effectiveness measurement	Not applicable, this is the first RMP.
Impact of risk minimisation	Not applicable, this is the first RMP.
Comment	/

V.2 Risk minimisation measure failure (if applicable)

Not applicable. This is the first RMP.

V.3 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Antibiotic associated colitis	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use	None proposed

	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, <Invented name> should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation. **Section 4.8**. Undesirable effects Listed as: Antibiotic-associated colitis (Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)) The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
Renal impairment and risk of convulsions	(Proposed) content in SPC **Section 4.2** Posology and method of Administration 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. **Section 4.4** Special warnings and precautions for use Convulsions may occur in patients with impaired renal function or in those receiving high doses **Section 4.8** Undesirable effects Listed as Convulsions **Section 4.9** Overdose Convulsions may occur in patients with impaired renal function or in those receiving high doses. The similar content is proposed also in corresponding sections of PIL.	None proposed

	Prescription only medicine.	
Interaction with oral anticoagulants	Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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). **Section 4.5** Interaction with other medicinal products and other forms of interaction 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). **Section 4.8** Undesirable effects Listed as Prolongation of bleeding time and prothrombin time The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Patients with reduced urine output	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral	None proposed

	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). **Section 4.8** Undesirable effects Listed as Crystalluria **Section 4.9** Overdose Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4). The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
False positivity of laboratory findings	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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 <Invented name> 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	None proposed

	results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods. The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
Serious allergic skin reactions (including acute generalised exanthemous pustulosis - AGEP)	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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 <Invented name> discontinuation and contra-indicates any subsequent administration of amoxicillin. **Section 4.8** Undesirable effects Listed as Stevens-Johnson syndrome Toxic epidermal necrolysis Bullous exfoliative-dermatitis Acute generalised exanthemous pustulosis (AGEP) The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Hypersensitivity reaction to any penicillins and history of sever immediate hypersensitivity reaction to another beta-lactam agent (cephalosporin, carbapenem, monobactam)	Proposed) content in SPC **Section 4.3** Contraindications History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam). **Section 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	None proposed

	and 4.8). **Section 4.8** Undesirable effects Listed asAngioneurotic oedema, Anaphylaxis, Serum sickness-like syndrome, Hypersensitivity vasculitis The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
Hepatic impairment and history of hepatic impairment due to amoxicillin/clavulanic acid	(Proposed) content in SPC **Section 4.2** Posology and method of administration Patients with hepatic impairment Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4)**Section 4.3** Contraindications History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8). **Section 4.4** Special warnings and precautions for use 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). Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable	None proposed

	during prolonged therapy. **Section 4.8** Undesirable effects Listed as: Rises in AST and/or ALT5, Hepatitis, Cholestatic jaundice The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
Haematological ADRs (leucopenia, agranulocytosis)	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy. **Section 4.8** Undesirable effects Listed as: reversible leucopenia (including neutropenia), reversible agranulocytosis The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Occurrence of a morbilliform rash if Amoxicillin/clavulanic acid is used in infectious mononucleosis	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use 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. **Section 4.8** Undesirable effects Listed as rash. The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
Overgrowth of non-susceptible organisms and antibiotic resistence – prolonged use	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use Prolonged use may occasionally result in overgrowth of non-susceptible organisms. **Section 4.8** Undesirable effects Listed as: Overgrowth of non-susceptible organisms	None proposed

	The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
Concomitant use with allopurinol	(Proposed) content in SPC **Section 4.4** Special warnings and precautions for use Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Concomitant use with methotrexate	(Proposed) content in SPC **Section 4.5** Interaction with other medicinal products and other forms of interaction Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Concomitant use with probenecid	(Proposed) content in SPC **Section 4.5** Interaction with other medicinal products and other forms of interaction 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. **Section 5.2** Pharmacokinetic properties Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5). The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Use in pregnancy and	(Proposed) content in SPC	None proposed

lactation	**Section 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. Brestfeeding 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. The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
Dosage of 7:1 ration presentations in patients with renal impairment with creatinine clearance less than 30 ml/min	(Proposed) content in SPC **Section 4**.2 Posology and method of Administration No clinical data are available for <Invented name> 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 <Invented name> 7:1 formulations for	None proposed

	patients under 2 months of age. Dosing recommendations in this population therefore cannot be made. In patients with creatinine clearance less than 30 ml/min, the use of <Invented name> presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available. The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	

1.8.2 clean	Amoxicillin trihydrate + Clavulanate potassium
Risk Management System	film-coated tablets

Part VI: Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary tables of Safety concerns

Important identified risks:	Antibiotic associated colitis
	Renal impairment and risk of convulsion
	Interaction with oral anticoagulants
	Patient with reduced urine output
	False positivity of laboratory findings
	Serious allergic skin reactions (including acute generalised exanthemous pustulosis - AGEP)
	Hypersensitivity reaction to any penicillins and history of sever immediate hypersensitivity reaction to another beta-lactam agent (cephalosporin, carbapenem, monobactam)
	Hepatic impairment and history of hepatic impairment due to amoxicillin/clavulanic acid
	Haematological ADRs (leucopenia, agranulocytosis)
	Occurrence of a morbilliform rash if Amoxicillin/clavulanic acid is used in infectious mononucleosis
Important potential risks:	Overgrowth of non-susceptible organisms and antibiotic resistance - prolonged use
	Concomitant use with allopurinol
	Concomitant use with methotrexate
	Concomitant use with probenecid
Missing information:	Use in pregnancy and lactation
	Dosage of 7:1 ration presentations in patients with renal impairment with creatinine clearance less than 30ml/min

1.8.2 clean	Amoxicillin trihydrate + Clavulanate potassium
Risk Management System	film-coated tablets

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorization efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimization measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Antibiotic associated colitis	(Proposed) content in SPC 4.4 Special warnings and precautions for use 4.8 Undesirable effects The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Renal impairment and risk of convulsions	(Proposed) content in SPC 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Interaction with oral anticoagulants	(Proposed) content in SPC 4.3 Contraindications 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects The similar content is proposed also in corresponding sections of PIL.	None proposed

	Prescription only medicine.	
Patients with reduced urine output	(Proposed) content in SPC 4.4 Special warnings and precautions for use 4.8 Undesirable effects 4.9 Overdose The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
False positivity of laboratory findings	(Proposed) content in SPC 4.4 Special warnings and precautions for use The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Serious allergic skin reactions (including acute generalised exanthemous pustulosis - AGEP)	(Proposed) content in SPC 4.4 Special warnings and precautions for use 4.8 Undesirable effects The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Hypersensitivity reaction to any penicillins and history of sever immediate hypersensitivity reaction to another beta-lactam agent (cephalosporin, carbapenem, monobactam)	(Proposed) content in SPC 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Hepatic impairment and history of hepatic impairment due to amoxicillin/clavulanic acid	(Proposed) content in SPC 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects The similar content is proposed also in corresponding sections	None proposed

	of PIL. **Prescription only medicine.**	
Haematological ADRs (leucopenia, agranulocytosis)	(Proposed) content in SPC 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Occurrence of a morbilliform rash if Amoxicillin/clavulanic acid is used in infectious mononucleosis	(Proposed) content in SPC 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects. The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	
Overgrowth of non-susceptible organisms and antibiotic resistence – prolonged use	(Proposed) content in SPC 4.4 Special warnings and precautions for use 4.8 Undesirable effects The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Concomitant use with allopurinol	(Proposed) content in SPC 4.2 Posology and method of administration 4.4 Special warnings and precautions for use The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Concomitant use with methotrexate	(Proposed) content in SPC 4.5 Interaction with other medicinal products and other forms of interaction The similar content is proposed also in corresponding sections of PIL.	None proposed

	Prescription only medicine.	
Concomitant use with probenecid	(Proposed) content in SPC 4.5 Interaction with other medicinal products and other forms of interaction 5.2 Pharmacokinetic properties The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Use in pregnancy and lactation	(Proposed) content in SPC 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed
Dosage of 7:1 ration presentations in patients with renal impairment with creatinine clearance less than 30 ml/min	(Proposed) content in SPC 4.2 Posology and method of administration The similar content is proposed also in corresponding sections of PIL. **Prescription only medicine.**	None proposed

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Sinus infection (Acute bacterial sinusitis)
Sinus infection (upper respiratory infection) is short-lived infection of the sinuses, air-filled passageways in the bones around the nose and eyes. Viruses cause most such infections. Viral illness can be complicated with bacterial infection. Approximately 0.5 % to 2% of viral sinusitis results in subsequent sinusitis caused by bacteria[1,2].

Middle ear infection (Acute otitis media)
Short-lived infection of the ear (Acute otitis media) is very common in childhood. Middle ear inflammation often begins when infections that cause sore throats, colds or other respiratory problems spread to the middle ear. It is the most common condition warranting medical therapy in children less than five years of age. Three out of four children will have at least one ear infection by their third birthday. Adults can also get ear infections, but they are less common. Viruses or bacteria can cause the inflammation. If bacteria are the cause, antibiotics should help.

Lower respiratory tract infection (Acute exacerbations of chronic bronchitis and Community acquired pneumonia)
These infections are bacterial worsening of chronic (long lasting) bronchitis and bacterial pneumonia. The first one is inflammation of the airways that carry air to lungs. It causes a cough that often brings up mucus, as well as shortness of breath, wheezing, and chest tightness. Chronic bronchitis is seen in 3.4% to 22.0% of adults. This wide range of prevalence estimates may be due to varying definition[3].

Pneumonia is an infection in one or both of the lungs. People most at risk are older than 65 or younger than 2 years of age, or already have health problems. Community-acquired pneumonia (an infection of the lungs that is caught outside of hospital) is a common disease, with an annual incidence of 5 to 11 cases per thousand adults[4].

Urinary tract infections (Cystitis and pyelonephritis)
Cystitis is an urinary bladder inflammation. It is most commonly caused by a bacterial infection. In women, urinary tract infections are the most common form of bacterial infection with 10% developing urinary tract infections yearly. Urinary tract infections occur four times more frequently in females than males. Recurrences are common, with nearly half of people getting a second infection within a year.
A predisposition for bladder infections may run in families. Other risk factors include diabetes, being uncircumcised, and having a large prostate.
Pyelonephritis (a kidney infection) is a severe bacterial infection that affects upper part of the urinary tract. Pyelonephritis occurs between 20–30 times less frequently than cystitis.

Skin and soft tissue infections including dental infections
Skin infections are folliculitis (folliculitis is inflammation of one or more hair follicles. It can occur anywhere on the skin), cellulitis (inflammation of the deeper layers of the skin), erysipelas (inflammation of the upper layers of the skin). The bacteria enter the body when one get an injury such as a bruise, burn, surgical cut, animal bites or wound. The epidemiology is less completely defined and may differ from those in industrialized countries and in developing countries.

Bone and joint infections, in particular osteomyelitis
Like other parts of the body, bones and joints can get infected. The infections are usually bacterial, but can also be fungal. They may spread to the bone or joint from nearby skin or muscles, from another part of the body through the bloodstream or by direct contamination if you have broken a bone so severely that part of it is sticking out through your skin. Direct contamination can also occur during surgeries to replace joints or repair fractures. In children, osteomyelitis most commonly affects the long bones of the legs and upper arm, while adults are more likely to develop osteomyelitis in the bones that make up the spine (vertebrae). People who have diabetes may develop osteomyelitis in their feet if they have foot ulcers. You may also be at risk if you are having hemodialysis.

VI.2.2 Summary of treatment benefits

The combination of amoxicillin and clavulanic acid is used to treat certain infections caused by bacteria, including dental infections, infections of the ears, lungs, sinus, skin, bones, joints and urinary tract. Amoxicillin is in a class of medications called penicillin-like antibiotics. It works by stopping the growth of bacteria. Clavulanic acid is in a class of medications called beta-lactamase inhibitors. It works by preventing bacteria from destroying amoxicillin. Antibiotics will not work for colds, flu, or other viral infections. Amoxicillin/clavulanic acid is available as 500 mg/125 mg film-coated tablet, 875 mg/125 mg and 400 mg/57 mg/5 ml powder for oral suspension. The medicine can only be obtained with a prescription.
Prescribers should consider official guidance on the use of antibacterial agents and local levels of resistance (resistance of a bacteria to an antibiotic that was originally effective for treatment of infections caused by it) to antibiotics. The combination of amoxicillin and clavulanic acid is prescribed when doctor presumed that causative bacteria could be resistant to amoxicillin alone or there is a possibility that the infection is caused by several different bacteria.
Amoxicillin/clavulanic acid was as effective as the comparator antibiotics (in many studies) for upper respiratory tract infections (~90 %), lower respiratory tract infections, urinary tract, skin and soft tissue infections. The main measure of effectiveness was the proportion of patients who were cured at the end of treatment as determined by a reduction in symptoms and reduction of bacteria[5].

VI.2.3 Unknowns relating to treatment benefits

The substance levofloxacinhas been used for many years. Many studies have been performed and a lot of data have been obtained from the patients treated with this drug. The safety of levofloxacin is essentially comparable to that of standard therapies for patients receiving the currently registered dosage and for whom contraindications and precautions of use (as in the product label) are taken into account.
The substance amoxicillin/clavulanic acid has been used for many years to successfully treat different infections. Many studies have been performed and a lot of data have been obtained from the patients treated with this drug. The patients with special conditions, such as liver disease, allergic reactions, an inflammation of the gut associated with diarrhea are considered to be well evaluated.
Data on the use of this medicine during pregnancy in humans is limited. Therefore use of this medicine should be avoided during pregnancy, unless considered essential by the physician.
Both substances are excreted into breast milk. Consequently, diarrhoea and fungal infections are possible in the breast-fed infant. Therefore use of this medicine should be avoided during breastfeeding, unless considered essential by the physician.
In patients with stage 4 kidney disease (creatinine clearance less than 30 ml/min), the use of this medicine is not recommended, as no recommendations for dose adjustments are available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Inflammation of the large intestine associated with the use of antibiotics	Antibiotic-associated colitis is an inflammation of the intestines that sometimes occurs following antibiotic	If you or your child experience inflammation of the large intestine, causing watery

(medications to treat infections caused by bacteria) **(Antibiotic associated colitis)**	treatment and is caused by toxins produced by the bacterium *Clostridium difficile*. When most of the other intestinal bacteria have been killed, *Clostridium difficile* grows rapidly and releases toxins that damage the intestinal wall. The disease and symptoms are caused by these toxins, not by the bacterium itself. Symptoms of antibiotic-associated colitis usually begin four to ten days after antibiotic treatment has begun. The early signs and symptoms of this disease include lower abdominal cramps, an increased need to pass stool, and watery diarrhea. As the disease progresses, the patient may experience a general ill feeling, fatigue, abdominal pain, and fever. If the disease proceeds to a more severe form (pseudomembranous enterocolitis), the patient may also experience nausea, vomiting, large amounts of watery diarrhea, and a very high fever (104-105°F/40-40.5°C).	diarrhoea usually with blood and mucus, stomach pain and/or fever you or your child need to stop taking the medicine and contact a doctor immediately so that an appropriate therapy can be initiated.
Kidney problems and the risk of convulsions **(Renal impairment and risk of convulsion)**	This medicine is excreted mostly by the kidney. The kidneys are a vital organ because they remove waste products from the blood. Kidney problems (Renal impairment) may be the result of a variety of diseases. A lessening of the kidney function leads to buildup of these waste products and can lead to kidney failure if left unchecked. Also, in patients with reduced urine output the formation of crystals in the urine (crystalluria) has been observed and this too can lead to renal failure. As the toxins continue to build-up in the body, convulsions can occur. Additionally, convulsions can occur also in people taking high doses of this medicine.	If you or your child has kidney problems the dose might be changed. A different strength or a different medicine may be chosen by your doctor. Your doctor might be monitoring you or your child for crystals in urine. Contact a doctor immediately if you or your child experience convulsions.
Interaction with medicines that you take orally to help stop blood clots from forming **(Interaction with oral anticoagulants)**	Medicines that you take orally to help stop blood clots from forming (Oral anticoagulants) and penicillin antibiotics (such as the medicine you have been prescribed) have been widely used in practice without reports of interaction. However, in the literature cases of slower blood clot	Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take medicines that help stop blood clots from forming as extra blood tests may be needed and adjustments of the dose of oral anticoagulants may

	formation (increased international normalised ratio) have been found. If you need to take both kinds of medicine together, the markers used to determine the clotting tendency of blood (prothrombin time or international normalised ratio) should be carefully monitored to see if adjustments of the dose of oral anticoagulants may be necessary.	be necessary. Contact a doctor immediately if you notice that your or your child's blood takes longer to clot.
Patients who are not passing water regularly **(Patients with reduced urine output)**	In patients who are not passing water regularly, formation of crystals in the urine (crystalluria) has been observed very rarely, predominantly when this medicine is given by injection. When high doses of this medicine are given, it is advisable that you drink enough so that you are passing urine regularly. This helps reduce the possibility of formation of crystals in the urine (amoxicillin crystalluria). In patients with bladder catheters, a regular check of patency should be maintained.	Talk to your doctor or pharmacist before taking this medicine if you are not passing water regularly. When high doses of this medicine are given, it is important that you drink enough in order to reduce the possibility of formation of crystals in the urine caused by the medicine (amoxicillin crystalluria). If you have a bladder catheter, a regular check of patency should be maintained.
Faulty laboratory test results **(False positivity of laboratory findings)**	During treatment with this medicine your laboratory test results may indicate the presence of glucose in urine. The presence of this medicine may falsely indicate that you have an immune-mediated disease with antibodies against red blood cells (false positive Coombs test). Also, when using this medicine you may falsely test positive for a fungal infection (Aspergillus infection). Enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine and other test results (Coombs, test for aspergillosis) need to be interpreted cautiously.	If you or your child is 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 or your child is taking this medicine. This is because this medicine can affect the results of these types of tests.
Serious allergic skin reactions (including acute generalised exanthemous pustulosis - AGEP)	Allergic skin reactions have been reported to occur with this medicine: Skin rash, itchiness, and hives (Urticaria) are uncommon skin reactions that may affect up to 1 in 100 people. Erythema multiforme is a rare skin condition which looks like small	If you notice a 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), you need to contact a doctor urgently.

	targets (central dark spots surrounded by a paler area, with a dark ring around the edge), that may affect up to 1 in 1,000 people, while the frequency of the life-threatening skin conditions Stevens-Johnson syndrome, which looks like a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals and the even more severe form, Toxic epidermal necrolysis, causing extensive peeling of the skin (more than 30% of the body surface), Bullous exfoliative-dermatitis, a widespread red skin rash with small pus-containing blisters, and acute generalised exanthemous pustulosis (AGEP), a red, scaly rash with bumps under the skin and blisters, are not known.	Other serious skin reactions are: - 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) - acute generalised exanthemous pustulosis (AGEP), a red, scaly rash with bumps under the skin and blisters. These reactions require the discontinuation of the medicine and contra-indicates any subsequent administration of amoxicillin, its active ingredient.
Hypersensitivity to any antibiotic of this class or a past severe immediate hypersensitivity reaction to a similar class of antibiotics **(Hypersensitivity reaction to any penicillins and history of sever immediate hypersensitivity reaction to another beta-lactam agent (cephalosporin, carbapenem, monobactam)**	Hypersensitivity reaction refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. The combination of the two active ingredients of this medicine, amoxicillin and clavulanate, is a commonly used antibiotic which is active against many bacterial organisms that cause different infections. The combination consists of amoxicillin which belongs to the antibiotic class of penicillin, and clavulanate, which inhibits beta lactamase, the main bacterial enzyme responsible for penicillin resistance. A penicillin allergy is an allergic reaction that occurs when the body's	Before initiating therapy with this medicine (amoxicillin/clavulanic acid), careful inquiry should be made regarding previous hypersensitivity reactions to other antibiotics of the same or similar classes (penicillins, cephalosporins, carbapenems or monobactams). If an allergic reaction occurs, the medicine should be discontinued and appropriate therapy instituted. Do not take the medicine - if you are allergic (hypersensitive) to amoxicillin, clavulanic acid, penicillin or any of the other ingredients of this medicine;

	immune system overreacts to penicillin and related antibiotics. Common allergic reactions to penicillin include rashes, hives, itchy eyes, and swollen lips, tongue, or face. In rare cases, an allergy to penicillin can cause a serious allergic reaction that is rapid in onset and may cause death (anaphylactic reaction). Symptoms include difficulty breathing, hives, wheezing, dizziness, loss of consciousness, rapid or weak pulse, skin turning blue, diarrhea, nausea, and vomiting. Penicillin antibiotics are the most common cause of drug allergies, with about 10 in 100 people reporting an allergy. Mild to moderate allergic reactions to penicillins may affect up to 5 in 100 people. Some people who are allergic to penicillin are also allergic to other closely related antibiotics, including cephalosporins, carbapenems and monobactams. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with amoxicillin/clavulanic acid, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or monobactams. If an allergic reaction occurs, amoxicillin/clavulanic acid should be discontinued and appropriate therapy instituted.	- 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. Allergic reactions that can be caused by this medicine: - 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. Allergic reactions can sometimes occur delayed. Contact a doctor immediately if you get any of these symptoms. Stop taking the medicine.
Liver problems or liver problems in the past due to this antibiotic (amoxicillin/clavulanic acid) **(Hepatic impairment and history of hepatic impairment due to amoxicillin/clavulanic acid)**	Liver disease is any disturbance of liver function that causes illness. The liver is responsible for many critical functions within the body and should it become diseased or injured, the loss of those functions can cause significant damage to the body. The medicine you are taking (Amoxicillin/clavulanate) is currently the most common cause of clinically apparent, drug induced acute liver	Do not take this medicine if you have ever had liver problems or jaundice (yellowing of the skin) when taking an antibiotic. Talk to your doctor or pharmacist before taking this medicine if you are being treated for liver problems. If you have liver problems you

	problems (injury/inflammation of the liver and jaundice (yellowing of the skin)) both in the United States and Europe. Liver problems are usually reversible; however, deaths have been reported. Amoxicillin is associated with a very low rate of mild liver problems when used alone. When amoxicillin is combined with the clavulanic acid, the estimated risk of liver problems increases from 3 to 17 people out of 100.000 people who have been prescribed this medication presumably due to the clavulanate component. Men over the age of 50 appear to be at increased risk of liver problems as are patients who receive prolonged or repeated courses of treatment. A delayed liver injury pattern has typically been reported with this medication that usually has a benign course and resolves within 2 months. Liver function should be monitored at regular intervals in patients with hepatic problems.	may have more frequent blood tests to check how your liver is working. Increase in some substances (enzymes) produced by the liver may show up in your blood tests. Contact a doctor immediately if you get any of these symptoms: - inflammation of the liver (hepatitis); - jaundice (yellowing of the skin and whites of the eyes), caused by increases in the blood of bilirubin (a substance produced in the liver).
Severe reduction in the number of white blood cells (**leucopenia, agranulocytosis**)	Agranulocytosis is a rare condition that occurs when the bone marrow does not make enough neutrophils, the white blood cells needed to fight infections. Agranulocytosis can turn minor infections into serious ones. Amoxicillin/clavulanic acid can cause this adverse reaction. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena (some kind of alergic reaction).	Periodic assessment of number of blood cells is advisable during prolonged therapy.
Occurrence of a morbilliform rash if Amoxicillin/clavulanic acid is used in infectious mononucleosis (Infectious mononucleosis - glandular fever, is an infection caused by the Epstein-Barr virus. The virus spreads through saliva, which is why it's sometimes called "kissing disease")	Certain type of rash (morbilliform rash) may appear, if the patient has mononucleosis while taking amoxicillin.	Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected.

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
Increases in number of bacteria, that do not respond to this antibiotic – prolonged use **(Overgrowth of non-susceptible organisms and antibiotic resistence – prolonged use)**	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. You need every dose to help fight the infection. If some bacteria survive they can cause the infection to come back.
Concomitant use with allopurinol, a medicine used for gout **(Concomitant use with allopurinol)**	If you are taking allopurinol (used for gout) with this medicine, it may be more likely that you'll have an allergic skin reaction.
Concomitant use with methotrexate, a medicine used to treat cancer or rheumatic diseases **(Concomitant use with methotrexate)**	Certain antibiotics such as the medicine you are taking (Penicillins) may reduce the excretion of methotrexate (a medicine used to treat cancer or rheumatic diseases), causing a potential increase in methotrexate toxicity. This medicine can affect how methotrexate (a medicine used to treat cancer or rheumatic diseases) works.
Concomitant use with probenecid, a medicine used for gout **(Concomitant use with probenecid)**	Concomitant use of probenecid (used for gout) is not recommended. Probenecid decreases the excretion of this medicine in urine. Therefore, concomitant use of probenecid may result in increased and prolonged blood levels of this medicine. If you are taking probenecid (used for gout), your doctor may decide to adjust the dose of this medicine.

Missing information

Risk	What is known
Use in pregnancy and lactation	<u>Pregnancy</u> Animal studies do not indicate any harmful effects with this medicine. Data on the use of this medicine during pregnancy in humans is limited; however, it does not indicate an increased risk of congenital malformations. In a single study in women giving birth prematurely this medicine was associated with an increased risk of necrotising enterocolitis in neonates, a condition when tissue in the small or large intestine is injured or begins to die off, which is considered to be the most common and serious intestinal disease among preemies. Therefore use of this medicine should be avoided during pregnancy, unless considered essential by the

	physician. Breastfeeding Both substances are excreted into breast milk. Consequently, diarrhoea and fungal infections are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Therefore use of this medicine should be avoided during breastfeeding, unless considered essential by the physician.
Dosage of this medicine in patients with stage 4 kidney disease **(Dosage of 7:1 ration presentations in patients with renal impairment with creatinine clearance less than 30 ml/min)**	In patients with stage 4 kidney disease (creatinine clearance less than 30 ml/min), the use of this medicine is not recommended, as no recommendations for dose adjustments are available.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for this product can be found at the national agency's internet page.

This medicine has no additional risk minimisation measures

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable. No postauthorisation studies are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable, this is the first Risk management plan.

Part VII- Annexes

ANNEX 1 EudraVigilance

Not applicable

ANNEX 2 Current or proposed SmPC/PIL

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 500 mg/125 mg film-coated tablets
<Invented name> 875 mg/125 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Invented name> 500 mg/125 mg film-coated tablets
Each film-coated tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid (as potassium clavulanate).

<Invented name> 875 mg/125 mg film-coated tablets
Each film-coated tablet contains 875 mg amoxicillin as (amoxicillin trihydrate) and 125 mg of clavulanic acid (as potassium clavulanate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

500 mg/125 mg: White coloured capsule shaped film coated tablet debossed with "I 06" on one side and plain on other side, tablet length: 19.40 ± 0.10 mm.
875 mg/125 mg: White coloured capsule shaped film coated tablet debossed with "I 07" on one side and plain on other side, tablet length: 21.70 ± 0.10mm.

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).

Dosages for 500 mg/125 mg amoxicillin/clavulanic acid
For adults and children ≥ 40 kg, this formulation of <Invented name> provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, this formulation of <Invented name> provides a maximum daily dose of 2400 mg amoxicillin/600 mg clavulanic acid, when administered as recommended below.

Dosages for 875 mg/125 mg amoxicillin/clavulanic acid
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, this formulation of <Invented name> provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered as recommended below.

If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of amoxicillin/clavulanic acid is 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 for 500 mg/125 mg amoxicillin/clavulanic acid:
- one 500 mg/125 mg dose taken three times a day;

Recommended doses for 875 mg/125 mg amoxicillin/clavulanic acid
- 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.

Paediatric population
Children < 40 kg

Children may be treated with <Invented name> tablets and suspensions.
Recommended doses for 500 mg/125 mg amoxicillin/clavulanic acid:
- 20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

As the tablets cannot be divided children weighing less than 25 kg must not be treated with <Invented name> tablets. Children aged 6 years and below should preferably be treated with <Invented name> suspension.

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 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)	12.5	14.3	16.7	20.0	6.67 – 20
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.67 - 5

Children aged 6 years and below or weighing less than 25 kg should preferably be treated with <Invented name> suspension.

No clinical data are available on doses of <Invented name> 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years.

Recommended doses for 875 mg/125 mg amoxicillin/clavulanic acid
- 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).

No clinical data are available for <Invented name> 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 <Invented name> 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Elderly patients
No dose adjustment is considered necessary.

Patients with renal impairment

500 mg/125 mg film-coated tablets
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 ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).

CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

875 mg/125 mg film-coated tablets
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 <Invented name> presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Patients with 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.

4.3 Contraindications

Hypersensitivity to the active substances 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 organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of <Invented name> 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 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 <Invented name> 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, <Invented name> 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 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 <Invented name> 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-*Aspergillu*s 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.

Breast-feeding
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 <Invented name>, sorted by MedDRA System Organ Class are listed below.

- 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)

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

System organ class	Adverse reactions
Hepatobiliary disorders	
Uncommon	Rises in AST and/or ALT5
Not known	Hepatitis[6] Cholestatic jaundice[6]
Skin and subcutaneous tissue disorders[7]	
Uncommon	Skin rash Pruritus Urticaria
Rare	Erythema multiforme
Not known	Stevens-Johnson syndrome Toxic epidermal necrolysis Bullous exfoliative-dermatitis Acute generalised exanthemous pustulosis (AGEP)[9]
Renal and urinary disorders	
Not known	Interstitial nephritis Crystalluria[8]

[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 <Invented name> 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 4.3
[10] See section 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
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). 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.

Management
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: Antibacterials for systemic use, 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) £
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 (Tmax) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times 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 500/125 mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 ± 0.83	1.5 (1.0-2.0)	15.72 ± 3.86	0.98 ± 0.12
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

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)	Cmax (µg/ml)	Tmax * (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 single 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 <Invented name> or its components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- *Tablet core*

Cellulose, microcrystalline (E460)
Sodium starch glycolate (type A)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

- *Film coating*

Titanium dioxide (E171)
Hypromellose (E464)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Strip (Alu/Alu): 10, 12, 14, 16, 20, 21, 24, 30, 100 or 500 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

PACKAGE LEAFLET

Package leaflet: Information for the patient

<Invented name> 500 mg/125 mg film-coated tablets
<Invented name> 875 mg/125 mg film-coated tablets
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 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

<Invented name> is an antibiotic and works by killing bacteria that cause infections. It contains two different active ingredients 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 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 or your child. 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 <Invented name> 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 or your child's infection. Depending on the results, you or your child 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 or your child is 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 or your child is 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 or your child is 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 or your child is taking, have recently taken or might take any other medicines.
If you are taking allopurinol (used for gout) with <Invented name>, it may be more likely that you'll 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.

<Invented name> with food, drink
Take <Invented name> at the start of a meal or slightly before and swallow the tablets whole with a glass of water.

Pregnancy, breast-feeding and fertility
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.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
<Invented name> can have side effects and the symptoms may make you unfit to drive.
Don't 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
500 mg/125 mg film-coated tablets
The usual dose is:
- 1 tablet three times a day

875 mg/125 mg film-coated tablets
- Usual dose – 1 tablet two times a day
- Higher dose – 1 tablet three times a day

Use in children
Children weighing less than 40 kg
Children aged 6 years or less should preferably be treated with amoxicillin/clavulanic acid oral suspension.

500 mg/125 mg film-coated tablets
Ask your doctor or pharmacist for advice when giving <Invented name> tablets to children weighing less than 40 kg. The tablets are not suitable for children weighing less than 25 kg.

875 mg/125 mg film-coated tablets
Ask your doctor or pharmacist for advice when giving <Invented name> tablets 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 or your chlid has kidney problems the dose might be changed. A different strength or a different medicine may be chosen by your doctor.
- If you or your child has liver problems you may have more frequent blood tests to check how your liver is working.

How to take <Invented name>
- Swallow the tablets whole with a glass of water at the start of a meal or slightly before
- 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 or your child still feels 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 or bottle to show the doctor.

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

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: may affect more than 1 in 10 people
- diarrhoea (in adults)

Common: 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: 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: 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 packaging after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

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.

6. Contents of the pack and other information

What <Invented name> contains
- The active substances are amoxicillin and clavulanic acid.
  <Invented name> 500 mg/125 mg film-coated tablets
  Each film-coated tablet contains 500 mg amoxicillin (as amoxicillin trihydrate) and 125 mg of

clavulanic acid (as potassium clavulanate).
<Invented name> 875 mg/125 mg film-coated tablets
Each film-coated tablet contains 875 mg amoxicillin as (amoxicillin trihydrate) and 125 mg of clavulanic acid (as potassium clavulanate).

- The other ingredients (excipients) are microcrystalline cellulose (E460), sodium starch glycolate (type A), colloidal anhydrous silica (E551) and magnesium stearate (E470b) in the tablet core and titanium dioxide (E171), hypromellose (E464) and macrogol in the film coating.

What <Invented name> looks like and contents of the pack
<Invented name> 500 mg/125 mg film-coated tablets
White coloured capsule shaped film coated tablet (tablet) debossed with "I 06" on one side and plain on other side, tablet length: 19.40 ± 0.10 mm.
<Invented name> 875 mg/125 mg film-coated tablets
White coloured capsule shaped film coated tablet (tablet) debossed with "I 07" on one side and plain on other side, tablet length: 21.70 ± 0.10mm.

<Invented name> is available in boxes of 10, 12, 14, 16, 20, 21, 24, 30, 100 or 500 film-coated tablets in strips.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

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 [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. Check with your doctor or pharmacist if you are not sure.
2. Do not take an antibiotic unless it has been prescribed specifically for you and only for the infection it was prescribed.
3. Do not take antibiotics that have been prescribed for other people even if they had an infection that was similar to yours.
4. Do not give antibiotics prescribed for you to other people.
5. If you have any antibiotic left over when you have taken the course as prescribed you should take the remainder to a pharmacy for appropriate disposal.

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 400 mg/57 mg in 5 ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml of suspension contains 400 mg amoxicillin (as amoxicillin trihydrate) and 57 mg clavulanic acid (as potassium clavulanate).
1 ml of suspension contains 80 mg amoxicillin (as amoxicillin trihydrate) and 11.4 mg clavulanic acid (as potassium clavulanate).

Excipient(s) with known effect:
5 ml of suspension contains 12.5 mg aspartame (E951). 1 ml of suspension contains 2.5 mg aspartame (E951).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

White to off-white powder.

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 children < 40 kg, this formulation of <Invented name> provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered as recommended below.

If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of amoxicillin/clavulanic acid is 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).

Children ≥ 40 kg should be treated with the adult formulations of <Invented name>.

Paediatric population
Children < 40 kg

Children may be treated with <Invented name> tablets and suspensions.
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).

No clinical data are available for <Invented name> 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 <Invented name> 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Elderly patients
No dose adjustment is considered necessary.

Patients with 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.

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

Patients with 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.

For instructions on dilution of the medicinal product before administration, see section 6.6.
The oral suspension is white to off-white with fruity aromatic odor.

4.3 Contraindications

Hypersensitivity to the active substances 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 organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of <Invented name> 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 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 <Invented name> 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, <Invented name> 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 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 <Invented name> 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-*Aspergillu*s 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.

<Invented name> contains aspartame (E951). Aspartame contains a source of phenylalanine. May be harmful for people with phenylketonuria.

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.

Breast-feeding

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 <Invented name>, sorted by MedDRA System Organ Class are listed below.

- 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)

System organ class	Adverse reactions
Infections and infestations	
Common	Mucocutaneous candidosis
Not known	Overgrowth of non-susceptible organisms
Blood and lymphatic system disorders	
Rare	Reversible leucopenia (including neutropenia) Thrombocytopenia
Not known	Reversible agranulocytosis Haemolytic anaemia Prolongation of bleeding time and prothrombin time[1]
Immune system disorders[10]	
Not known	Angioneurotic oedema Anaphylaxis Serum sickness-like syndrome Hypersensitivity vasculitis
Nervous system disorders	
Uncommon	Dizziness Headache
Not known	Reversible hyperactivity Convulsions[2] Aseptic meningitis
Gastrointestinal disorders	
Common	Diarrhoea Nausea[3] Vomiting

System organ class	Adverse reactions
Uncommon	Indigestion
Not known	Antibiotic-associated colitis[4] Black hairy tongue Tooth discolouration[11]
Hepatobiliary disorders	
Uncommon	Rises in AST and/or ALT5
Not known	Hepatitis[6] Cholestatic jaundice[6]
Skin and subcutaneous tissue disorders	
Uncommon	Skin rash Pruritus Urticaria
Rare	Erythema multiforme
Not known	Stevens-Johnson syndrome Toxic epidermal necrolysis Bullous exfoliative-dermatitis Acute generalised exanthemous pustulosis (AGEP)[9]
Renal and urinary disorders	
Not known	Interstitial nephritis Crystalluria[8]

[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 <Invented name> 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 4.3
[10] See section 4.4
[11] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

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
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). 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.

Management
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: Antibacterials for systemic use, 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)£
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 (Tmax) 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	Cmax	Tmax *	AUC (0-24h)	T 1/2
	(mg)	(µg/ml)	(h)	((µg.h/ml)	(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 single <Invented name> 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 <Invented name> or its components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicon dioxide (E551)
Silica, colloidal anhydrous (E551)
Aspartame (E951)
Succinic acid (E363)
Xanthan gum (E415)
Hypromellose (E464)
Raspberry flavour
Orange flavour
Golden caramel

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before reconstitution: 3 years
After reconstitution: After reconstitution, the product should be used within 7 days. Store in a refrigerator (2°C – 8°C).

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

HDPE bottle with marking for level of reconstitution, polypropylene CRC cap: 6 g, 12 g, 14 g or 20 g of powder for reconstitution of 30 ml, 60 ml, 70 ml or 100 ml of oral suspension, respectively, in a

box. Packs are supplied with a 5 ml polystyrene oral syringe graduated from 0.5 ml to 5 ml in 0.5 ml increments.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Check cap seal is intact before using. Shake bottle to loosen powder. Fill the bottle with drinking water to just below the filling mark, close and shake well. After that add drinking water exactly to the filling mark and shake well again.

Shake the bottle every time before use.
The oral suspension is white to off-white with fruity aromatic odor.

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Package leaflet: Information for the patient

<Invented name> 400 mg/57 mg in 5 ml powder for oral suspension
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 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

<Invented name> is an antibiotic and works by killing bacteria that cause infections. It contains two different active ingredients 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 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 or your child. 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 <Invented name> 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 or your child's infection. Depending on the results, you or your child 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 or your child is 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 or your child is 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 or your child is 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 or your child is taking, have recently taken or might take any other medicines.
If you are taking allopurinol (used for gout) with <Invented name>, it may be more likely that you'll 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> can affect how mycophenolate mofetil (a medicine used to prevent the rejection of transplanted organs) works.

<Invented name> with food, drink
Take <Invented name> at the start of a meal or slightly before.

Pregnancy, breast-feeding and fertility
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.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
<Invented name> can have side effects and the symptoms may make you unfit to drive.
Don't drive or operate machinery unless you are feeling well.

Powder for oral suspension contains aspartame (E951)
Aspartame contains a source of phenylalanine. May be harmful for people with phenylketonuria.

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
This suspension is not usually recommended for adults and children weighing 40 kg and over. Ask your doctor or pharmacist for advice.

Use in children
Children weighing less than 40 kg

Children aged 6 years or less should preferably be treated with <Invented name> oral suspension
All doses are worked out depending on the child's bodyweight in kilograms.
- Your doctor will advise you how much <Invented name> you should give to your baby or child.
- Usual dose – 25 mg/3.6 mg to 45 mg/6.4 mg for each kilogram of body weight a day, given in two divided doses.
- Higher dose – up to 70 mg/10 mg for each kilogram of body weight a day, given in two divided doses.

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

How to take <Invented name>
- Always shake the bottle well before each dose.
- Give at the start of a meal or slightly before.
- 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 or your child still feels unwell you should go back to see the doctor.

Instructions for reconstitution of the <Invented name> 400 mg/57 mg in 5 ml powder for oral suspension:
- Check if cap seal is intact before use. Shake to loosen powder.
- Fill the bottle with drinking water to just below the filling mark.
- Close the botlle and shake well.
- Add drinking water exactly to the filling mark.
- Shake well again.

Shake the bottle every time before use.

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 or bottle to show the doctor.

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

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: may affect more than 1 in 10 people
- diarrhoea (in adults)

Common: 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: 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: 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
- stained teeth (in children), usually removed by brushing.

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 packaging after EXP. The expiry date refers to the last day of that month.

Before reconstitution
Do not store above 25°C.
Store in the original package in order to protect from moisture.
After reconstitution
Store in a refrigerator (2°C – 8°C).
After reconstitution, the product should be used within 7 days.

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.

6. Contents of the pack and other information

What <Invented name> contains
- The active substances are amoxicillin and clavulanic acid. 5 ml of suspension contains 400 mg amoxicillin (as amoxicillin trihydrate) and 57 mg clavulanic acid (as potassium clavulanate).
  1 ml of suspension contains 80 mg amoxicillin (as amoxicillin trihydrate) and 11.4 mg clavulanic acid (as potassium clavulanate).

- The other ingredients (excipients) are silicon dioxide (E551), colloidal anhydrous silica (E551), aspartame (E951), succinic acid (E363), xanthan gum (E415), hypromellose (E464), raspberry flavour, orange flavour and golden caramel.

What <Invented name> looks like and contents of the pack
White to off-white powder which on reconstitution with water gives white to off-white suspension with fruity aromatic odor.

<Invented name> is available in boxes of 6 g, 12 g, 14 g or 20 g of powder for reconstitution of 30 ml, 60 ml, 70 ml or 100 ml of oral suspension, respectively, in HDPE bottles. The bottles have a marking for level of reconstitution. Packs are supplied with a 5 ml polystyrene oral syringe graduated from 0.5 ml to 5 ml in 0.5 ml increments.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

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 [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. Check with your doctor or pharmacist if you are not sure.
2. Do not take an antibiotic unless it has been prescribed specifically for you and only for the infection it was prescribed.

3. Do not take antibiotics that have been prescribed for other people even if they had an infection that was similar to yours.
4. Do not give antibiotics prescribed for you to other people.
5. If you have any antibiotic left over when you have taken the course as prescribed you should take the remainder to a pharmacy for appropriate disposal.

ANNEX 3 Worldwide marketing status by country

Not applicable

ANNEX 4 Synopsis of clinical trial programme

Not applicable

ANNEX 5 Synopsis of pharmacoepidemiological study programme

Not applicable

ANNEX 6 Protocols for proposed and on-going studies in Part III

Not applicable

ANNEX 7 Specific adverse event follow-up forms

Not applicable

ANNEX 8 Protocols for studies in Part IV

Not applicable

ANNEX 9 Synopsis of newly available study reports in Parts III-IV

Not applicable

ANNEX 10 Details of proposed additional risk minimisation activities

Not applicable

ANNEX 11 Mock up examples

Not applicable

ANNEX 12 Other supporting data - Literature references

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[3] American Journal of Respiratory and Critical Care Medicine; V.187; 2/1/13; p228

[4] European Journal of Clinical Microbiology and Infectious Diseases; V.32; 3/13; p305

[5] Bax R. Development of a twice daily dosing regimen of amoxicillin/clavulanate. International Journal of Antimicrobial Agents; 30S (2007): S118–S121