SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AmoxiClav-Denk 500/62.5

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances: amoxicillin and clavulanic acid.
One film-coated tablet contains 574 mg amoxicillin trihydrate, equivalent to 500 mg amoxicillin and 74.45 mg potassium clavulanate, equivalent to 62.5 mg clavulanic acid.

Excipients with known effect: Each film-coated tablet contains 12.3 mg potassium and 15.6 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong film-coated tablets with a break-line on both sides.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AmoxiClav-Denk 500/62.5 is indicated in adults for the treatment of acute and chronic infections that are receptive to oral therapy. Gram-positive and gram-negative microorganisms are possible pathogens whose resistance to β-lactam antibiotics is caused by β-lactamases, which are however sensitive to the combination of amoxicillin and clavulanic acid.

If there is a reasonable suspicion that the afore-mentioned pathogens could be the cause of a certain infection, treatment with this combination can be commenced even before receiving the result of the antibiogram.

This medicine is suitable for treatment of the following indications:

- Infections of the upper and lower respiratory tract including:
  - otitis media
  - acute sinusitis
  - acute exacerbations of chronic bronchitis
  - pneumonia
- kidney and lower urinary tract infections
- genital infections

Please note:
Consideration should be given to official national and international guidelines on the appropriate use of antimicrobial agents.

4.2 Posology and method of administration

Posology
The dosage of amoxicillin/clavulanic acid depends on the age, weight and renal function of the individual patient, on the severity and site of infection and on the suspected or verified pathogens.

As a rule, it is the patient's body weight that is the deciding factor for determining dosage even if this is not in accordance with the given age in individual cases.

Adults are given 2 film-coated tablets 2-3 times a day.

Dosage in the elderly
As long as there is no evidence of renal or hepatic impairment, the dose is as for adults.

Dosage in hepatic impairment
Use of AmoxiClav-Denk 500/62.5 film-coated tablets is not permitted in patients with a history of hepatic impairment associated with previous treatment with amoxicillin/clavulanic acid. Treatment should be administered with caution to patients with symptoms of liver damage and liver function tests should be carried out at regular intervals. If the liver parameters deteriorate during therapy, a change of treatment should be considered. The experience in the use of the product is not adequate in order to give special dosage recommendations.

Dosage in renal impairment and in haemodialysis patients
The dosage for adult patients with a glomerular filtration rate/creatinine clearance of more than 30 ml/min is 2 film-coated tablets 2-3 times a day.
AmoxiClav-Denk 500/62.5 is contraindicated in dialysis patients and patients with a creatinine clearance of less than 30 ml/min.
If creatinine clearance ranges between 20 and 30 ml/min the normal dose should be reduced to 2/3, and to 1/3 in the case of a glomerular filtration rate/creatinine clearance between 10 and 20 ml/min. If necessary the dosage interval may be extended while controlling the serum level.

Method of administration
The film-coated tablets should be swallowed whole or in pieces with fluids, but should not be chewed.

They should be taken at the start of meals, after the first bite. This does not interfere with the efficacy of amoxicillin/clavulanic acid but it may minimise any possible gastrointestinal discomfort. However, AmoxiClav-Denk 500/62.5 film-coated tablets are also effective when taken before or after meals.

Please note:
As amoxicillin may precipitate in the bladder catheter if present in urine at high concentrations at room temperature, a regular check of patency should be maintained.

It is advisable to maintain adequate fluid intake during the administration of amoxicillin in order to prevent a possible crystalluria.

Patients with severe gastrointestinal disturbances with vomiting and/or diarrhoea should not be treated with oral AmoxiClav-Denk 500/62.5 film-coated tablets since adequate absorption cannot be guaranteed.

If one tablet is forgotten at the scheduled time, this should be taken as soon as possible. The next tablet should then be taken at the scheduled time. There should be an interval of at least 4 hours between taking two doses.

Duration of treatment
The treatment should depend on the age, weight and renal function of the individual patient and on the severity and indication and should take between 7 and 10 days. The doctor decides how long it should take. The treatment should be continued for a further 2 to 3 days after the clinical symptoms have abated.

The treatment should not exceed 14 days without review.

The kidney, liver and blood parameters should be monitored regularly during long-term treatment.

As a precaution, treatment over at least 10 days is indicated for the treatment of infections with β-haemolytic streptococci in order to guard against late complications (e.g. rheumatic fever, glomerulonephritis).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Amoxicillin/clavulanic acid is contraindicated in case of hypersensitivity to β-lactam antibiotics (e.g. penicillins, cephalosporins) owing to the danger of anaphylactic shock. Before initiating treatment careful inquiry should therefore be made concerning allergic reactions in the past (e.g. after receiving penicillin or cephalosporin).

Use of amoxicillin/clavulanic acid is not permitted in patients with a history of jaundice/liver impairment after previous treatment with this medicine.

4.4 Special warnings and precautions for use

- Caution is advised when treating the elderly (aged 60 and over) and liver function should be monitored (see 4.8 Adverse drug reactions) during treatment.
- Treatment should only be applied with caution in patients with pre-existing hepatic impairment. Liver function tests at regular intervals are indicated in patients with signs of liver damage. If the liver function deteriorates during therapy, discontinuation of treatment should be considered. Liver function tests should be carried out at regular intervals during treatment and up to two months after treatment cessation.
- Amoxicillin/clavulanic acid should be administered with caution to patients with severe allergies or asthma since such patients are more likely to respond with allergic reactions. The possibility of a cross allergy with other antibiotics such as cephalosporins should be considered.
- Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy.
- Patients with severe gastrointestinal disturbances with vomiting and/or diarrhoea should not be treated with oral amoxicillin/clavulanic acid since adequate absorption cannot be guaranteed. Parenteral treatment is recommended in this case.
- Amoxicillin/clavulanic acid is generally well tolerated and has low toxicity, as is characteristic for penicillins. However, during long-term treatment it is still advisable to monitor organ function on a regular basis such as renal, hepatic and haematopoietic function.
- The dosage must be adjusted in patients with renal impairment (please refer to 4.2. Posology and method of administration).
- As amoxicillin may precipitate in the bladder catheter if present in urine at high concentrations at room temperature, a regular check of patency should be maintained.
- In very rare cases, crystalluria may occur in patients with impaired diuresis, predominately with parenteral therapy. During the administration of high doses of medicines containing amoxicillin, it is advisable to maintain adequate fluid intake in order to reduce the possibility of crystalluria (see 4.9. Overdose).

- As with other broad-spectrum antibiotics, superinfections with resistant bacteria or yeasts may occur during long-term use.
- Patients with infectious mononucleosis (Pfeiffer's disease) and patients with lymphatic leukaemia have a significantly higher risk of developing morbilliform exanthema. Consequently, amoxicillin/clavulanic acid should not be administered to treat concomitantly occurring bacterial infections in patients with these conditions.
- Teeth discolouration can be prevented by carrying out intensive oral hygiene during treatment.
- The presence of clavulanic acid in amoxicillin/clavulanic acid may cause a non-specific binding of IgG and albumin to the red blood cells leading to a false positive Coombs test.

Acute life-threatening adverse drug reactions may occur during treatment with amoxicillin/clavulanic acid and treatment may therefore have to be discontinued prematurely, e.g.:
- pseudomembranous enterocolitis,
- severe, acute life-threatening hypersensitivity reactions,
- occurrence of (epilepsy-like) convulsions.

(Please also refer to 4.8 Adverse drug reactions and subsection Countermeasures in the event of life-threatening adverse drug reactions).

This medicine contains potassium and sodium.
Each film-coated tablet contains 12.3 mg potassium. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.
Each film-coated tablet contains 15.6 mg sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Bacteriostatic antibiotics and/or chemotherapeutics
Amoxicillin/clavulanic acid should not be combined with bacteriostatic chemotherapeutics/antibiotics (such as tetracyclines, macrolides, sulphonamides or chloramphenicol) since an antagonistic effect has been observed *in vitro*.

Probenecid
Concomitant administration of probenecid inhibits the tubular secretion of amoxicillin leading to higher and more prolonged levels of amoxicillin in the blood. This does not inhibit the excretion of clavulanic acid. Concomitant use of probenecid and amoxicillin/clavulanic acid is therefore not recommended.

Allopurinol
Simultaneous use of allopurinol during treatment with amoxicillin/clavulanic acid can promote the occurrence of allergic skin reactions.

Diuretics
The use of diuretics, particularly forced diuresis, accelerates the excretion of amoxicillin/clavulanic acid. This leads to a reduction of the active ingredient concentration of this antibiotic in the blood.

Digoxin
An increase in absorption of digoxin is possible on concurrent administration with amoxicillin/clavulanic acid.

Disulfiram
Amoxicillin/clavulanic acid should not be used concomitantly with disulfiram.

Anticoagulants
The tendency to bleed may be potentiated if anticoagulants of the coumarin class (e.g. warfarin) are administered concomitantly. Patients who are taking anticoagulants at the same time should therefore be monitored accordingly.

Hormonal contraceptives
As with other antibiotics, treatment with amoxicillin/clavulanic acid may affect the intestinal flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Supplementary non-hormonal birth control measures should therefore be taken.

Pregnancy
Temporary reduced levels of estradiol and its conjugates were diagnosed in pregnant women who received treatment with ampicillin. This effect may also occur with amoxicillin/clavulanic acid.

Effect on laboratory diagnostic examinations
The presence of clavulanic acid in amoxicillin/clavulanic acid may cause a non-specific binding of IgG and albumin to the red blood cells leading to a false positive Coombs test.
Non-enzymatic methods for glucose determination may yield false positive results.
Likewise, identification of urobilinogen may also be impaired.

Further interactions
Diarrhoea and vomiting may cause reduced absorption of amoxicillin/clavulanic acid as well as other medicines and thus adversely affect their efficacy.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is only limited information available on the use of amoxicillin/clavulanic acid during pregnancy. Both active ingredients pass to the embryo/foetus by way of the placenta. No adverse effects of amoxicillin/clavulanic acid on the health of the foetus/newborn child could be identified after use in pregnant women. However, a single study in women with premature rupture of the amnion reported that prophylactic treatment with amoxicillin/clavulanic acid can be associated with an increased risk of necrotising enterocolitis in neonates.
Like all medicines, amoxicillin/clavulanic acid should only be used during pregnancy if in the judgement of the doctor the potential benefits outweigh the possible risks.

Breast-feeding
Amoxicillin/clavulanic acid is permitted during the nursing period. Both active ingredients pass into breast milk. Consequently, diarrhoea and colonisation of the mucosae by yeasts are possible in the breastfed infant so that in some cases it may be necessary to wean the infant. The possibility of sensitisation should be taken into account.
Like all medicines, amoxicillin/clavulanic acid should only be administered during the nursing period if in the judgement of the doctor the potential benefits outweigh the possible risks.

4.7 Effects on ability to drive and use machines

Amoxicillin/clavulanic acid has been shown to have a minor or moderate influence on the ability to drive a vehicle and use machines.

Amoxicillin/clavulanic acid may sometimes be associated with adverse drug reactions such as dizziness or cerebral convulsions that may impair the ability to drive a vehicle, operate machines and/or work safely. This applies in particular in combination with alcohol (please also refer to 4.8 Adverse drug reactions).

4.8 Undesirable effects

Adverse drug reactions are classified as follows:
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)

The following adverse drug reactions have been observed after use of amoxicillin/clavulanic acid:

Infections
Common: Candidiasis of skin and mucosa.
Prolonged or repeated use of amoxicillin/clavulanic acid can result in a superinfection and colonisation with resistant bacteria or yeasts.

Blood and lymphatic system disorders
Rare: Reversible leukopenia (including neutropenia) and thrombocytopenia.
Very rare: Changes in blood count in form of granulocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia or myelosuppression and prolongation of the bleeding and prothrombin time. These manifestations are reversible after discontinuation of therapy.

Immune system disorders
Very rare: Severe allergic reactions resulting from sensitisation to 6-amino penicillic acid group, e.g. in the form of drug fever, eosinophilia, angioneurotic oedema (Quincke's edema), anaphylaxis, serum sickness, allergic vasculitis or nephritis and laryngeal oedema.

Hypersensitivity reactions of every severity, sometimes resulting in anaphylactic shock, have also been observed after oral administration of penicillins. Severe anaphylactoid reactions, which are considerably rarer after oral administration of penicillins than after intravenous or intramuscular administration, may require appropriate emergency measures (see Countermeasures in the event of life-threatening adverse drug reactions).

Nervous system disorders
Uncommon: Headache, dizziness.
Very rare: Reversible hyperactivity, anxiety, insomnia, confusion, aggression and cerebral convulsions. Cerebral convulsions may occur in patients with impaired renal function or in patients receiving high doses of amoxicillin/clavulanic acid (see 4.7 Effects on ability to drive and use machines).

Gastrointestinal disorders
Very common: Diarrhoea.
Common: Nausea (increases with higher dose), vomiting, gastrointestinal disturbances such as stomach ache, meteorism, soft stools. These are generally of a mild nature and usually recede during or upon discontinuation of treatment. Amoxicillin/clavulanic acid is tolerated better when taken with meals.
Uncommon: Dyspepsia.
Rare: Intestinal candidiasis.
Very rare: If severe persistent diarrhoea occurs during or in the first weeks after treatment, the possibility of pseudomembranous enterocolitis should be considered (in most cases caused by *Clostridium difficile*). This intestinal disease triggered by treatment with antibiotics may be life-threatening (please also refer to Countermeasures in the event of life-threatening adverse drug reactions). Black tongue.

In one individual study on women with premature amniorrhexis there were reports of prophylactic treatment with amoxicillin/clavulanic acid being associated with a higher risk of a necrotising enterocolitis in neonates.

Hepatobiliary disorders
Uncommon: Moderate, asymptomatic rise in liver enzyme values (AST, ALT, alkaline phosphatase). However, this is not necessarily a sign of liver damage caused by amoxicillin/clavulanic acid.
Very rare: Temporary hepatitis and cholestatic jaundice. These reactions have also been observed in association with other penicillins and cephalosporins.
Symptoms of liver impairment may occur during or shortly after treatment with amoxicillin/clavulanic acid. In some cases, however, they do not become apparent until several weeks after treatment cessation. Liver impairment may be severe and occurs predominately in males and elderly patients (aged 60 and over) or with treatment courses exceeding 14 days. It is usually reversible. However, in extremely rare cases a fatal outcome has been reported. These have mostly occurred in patients with a serious underlying illness or in patients taking other medicines at the same time.
Liver impairment also has been observed in children in very rare cases.

Skin and subcutaneous tissue disorders
Uncommon: Urticaria, pruritus, exanthema. The typical morbilliform exanthema occurs 5 to 11 days after the commencement of treatment. Patients with infectious mononucleosis and patients with lymphatic leukaemia have a higher risk of developing exanthema. An immediate skin reaction in the form of urticaria usually points to a real penicillin allergy and treatment must be discontinued. Furthermore, mucositis, particularly oral mucositis, may occur. Dry mouth and taste alteration may occur.
Rare: Erythema exsudativum multiforme.
Not known: Bullous or exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised pustular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS).

An antigen community may exist between yeasts and penicillin, which means that reactions to penicillin such as those after second administration may occur after initial administration of penicillin in patients with pre-existing mycosis.

Renal and urinary disorders
Very rare: Acute interstitial nephritis, crystalluria (see 4.9 Overdose).

General disorders and administration site conditions
Very rare: As seen with other antibiotics, teeth discolouration has been observed. Altered oral flora containing predominately microorganisms that excrete iron bearing substances are being discussed as a possible cause for this. These form deposits of iron sulphide on the teeth. This discolouration remained in about half of those patients affected (usually children under the age of 10) despite intensive oral hygiene.

Countermeasures in the event of life-threatening adverse drug reactions
The following extremely rare adverse drug reactions may be acutely life-threatening in some cases. A doctor should therefore be contacted immediately if such an incident occurs suddenly or progresses unexpectedly:

Severe, acute life-threatening hypersensitivity reactions
Treatment with amoxicillin/clavulanic acid must be discontinued immediately at the first signs of a hypersensitivity reaction and the appropriate emergency measures for the symptoms initiated (e.g. administration of antihistamines, corticosteroids, sympathomimetics and, if necessary, artificial ventilation) by qualified health care providers.

Pseudomembranous enterocolitis
Persisting severe diarrhoea during and following treatment with amoxicillin/clavulanic acid can be an

indication for a potentially life-threatening pseudomembranous enterocolitis. Immediate discontinuation of treatment with amoxicillin/clavulanic acid is generally required depending on the indication and, if necessary, appropriate treatment should be initiated by a doctor at once (such as administration of special antibiotics/chemotherapeutic agents whose clinical efficacy has been proven). Drugs that inhibit intestinal peristalsis are contraindicated.

Occurrence of (epilepsy-like) convulsions
The usual appropriate emergency measures are indicated (e.g. keeping airways free, anticonvulsants such as diazepam or barbiturates).

During the administration of high doses of amoxicillin/clavulanic acid it is advisable to maintain adequate fluid intake and output in order to minimise the possibility of amoxicillin crystalluria.

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.

4.9 Overdose

Symptoms of intoxication
The symptoms of overdose essentially match the adverse drug reaction profile (see 4.8 Adverse drug reactions).
Gastrointestinal symptoms and fluid and electrolyte imbalance may occur. Amoxicillin crystalluria may occur which can cause renal failure in some cases (see 4.4 Special warnings and precautions for use and 4.8 Adverse drug reactions).

As amoxicillin may precipitate in the bladder catheter if present in urine at high concentrations at room temperature, a regular check of patency should be maintained.

Treatment of intoxications
There is no specific antidote for an overdose. Treatment consists of symptomatic measures while paying particular attention to the water and electrolyte balance. Administration of medicinal charcoal and gastric lavage are only indicated in cases of very high overdose (> 250 mg/kg body weight). Amoxicillin/clavulanic acid can be eliminated by means of haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Amoxicillin is a semi-synthetic aminopenicillin that is not β-lactamase-resistant. Clavulanic acid is a β-lactamase inhibitor that is similar in structure to amoxicillin and other penicillins.

ATC-Code: J01 CR02

Mechanism of action
Amoxicillin acts by inhibiting the synthesis of bacterial cell walls (in the growth phase) by blocking the penicillin binding proteins (PBPs) such as the transpeptidases. This causes a bactericidal effect.

In combination with clavulanic acid amoxicillin is protected from inactivation by certain β-lactamases. Clavulanic acid protects amoxicillin from degradation by most β-lactamases of staphylococci as well as some plasmid-mediated β-lactamases (e.g. TEM, OXA) and certain chromosomally mediated β-lactamases of gram-negative bacteria. These β-lactamases are found for example in *Escherichia coli, Klebsiella* spp., *Proteus mirabilis* and *Haemophilus influenzae*. The antibacterial therapeutic spectrum

of amoxicillin is extended to include those bacteria whose β-lactamases can be inhibited by clavulanic acid.

Relation between pharmacokinetics and pharmacodynamics
The efficacy essentially depends on the length of time the peak plasma concentration is higher than the minimum inhibitory concentration of the pathogen.

Resistance mechanisms:
A resistance to amoxicillin/clavulanic acid may be due to the following mechanisms:

- Inactivation by β-lactamases: Amoxicillin/clavulanic acid is not effective against β-lactamase forming bacteria whose β-lactamases are not inhibited by clavulanic acid.
- Reduced affinity of PBPs to amoxicillin: In the case of pneumococci and other streptococci, acquired resistance to amoxicillin/clavulanic acid is caused by modifications of existing PBPs as a consequence of mutation. Methicillin (oxacillin)-resistant staphylococci are resistant to amoxicillin and other β-lactam antibiotics due to the formation of an additional PBP with reduced affinity.
- Inadequate penetration of the outer cell wall by amoxicillin may result in insufficient inhibition of PBPs in gram-negative bacteria.
- Amoxicillin can be actively transported out of the cell by efflux pumps.

There is partial or complete cross resistance between amoxicillin/clavulanic acid and penicillins, cephalosporins as well as other β-lactam/β-lactamase inhibitor combinations.

Limit values
Testing of amoxicillin/clavulanic acid is carried out using a dilution series of amoxicillin in the presence of a constant concentration of 2 mg/l clavulanic acid. The following minimum inhibitory concentrations have been established for susceptible and resistant pathogens:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) limit values

Pathogen	Susceptible	Resistant
Enterobacteriaceae	-	> 8 mg/l
Enterococcus spp.	≤ 4 mg/l	> 8 mg/l
Haemophilus influenzae	≤ 1 mg/l	> 1 mg/l
Moraxella catarrhalis	≤ 1 mg/l	> 1 mg/l
Neisseria meningitidis	≤ 0.12 mg/l	> 1 mg/l
Gram-negative anaerobes	≤ 4 mg/l	> 8 mg/l
Gram-positive anaerobes	≤ 4 mg/l	> 8 mg/l
Non species-specific limit values*	≤ 2 mg/l	> 8 mg/l

* Are based predominately on serum pharmacokinetics
The test result for Penicillin G is accepted for *Staphylococcus* ssp., *Streptococcus* ssp. (groups A, B, C, G) and *Streptococcus pneumoniae*.

Prevalence of acquired resistance
The prevalence of acquired resistance in some species may vary geographically and over time. Local information on resistance is therefore required, particularly for the adequate treatment of severe infections. Expert advice should be sought when the local prevalence of resistance is such that the efficacy of amoxicillin/clavulanic acid is questionable. Particularly in the case of severe infections or failure of therapy, a microbiological diagnosis with evidence of the pathogen and its susceptibility to amoxicillin/clavulanic acid should be sought.

5.2 Pharmacokinetic properties

Bioavailability
Both active components, amoxicillin and clavulanic acid are completely dissolved in aqueous solutions at physiological pH. When taken orally both components are rapidly and well absorbed. Absorption is optimal when amoxicillin/clavulanic acid is taken at the start of a meal.

Amoxicillin
The absolute bioavailability of amoxicillin depends on the dosage and ranges between approximately 72 % and 94 %. At a dosage range of 250 to 750 mg the bioavailability (parameter AUC and/or recovery in urine) is linearly proportional to dose. The relative absorption decreases at higher doses. Absorption is not affected by intake of food. Peak plasma concentrations are reached about 1 to 2 hours after oral administration of amoxicillin. The apparent distribution volume ranges between approximately 0.3 and 0.4 l/kg and binding to serum proteins is approximately 18 %. Amoxicillin diffuses through the placental barrier and a small fraction is eliminated into breast milk.

Amoxicillin is largely excreted through the kidneys (52 ± 15 % of a dose in unchanged form within 7 hours) and a small fraction is excreted in bile. Total clearance ranges between approximately 250 and 370 ml/min. The serum half-life in subjects with normal renal function is approximately 1 hour (0.9 – 1.2 h), in patients with creatinine clearance ranging between 10 and 30 ml/min it is about 6 hours and in anuria it ranges between 10 and 15 hours. After a single oral dose of 500/125 mg amoxicillin/clavulanic acid the average minimal plasma concentration (after 8 hours) of amoxicillin was 0.3 mg/l. Amoxicillin can be eliminated by means of haemodialysis.

Clavulanic acid
The absolute bioavailability of clavulanic acid of approximately 60 % differs markedly from individual to individual. Absorption is highest when taken just before meals. Peak plasma concentrations of clavulanic acid are present approximately 1 to 2 hours after oral application. The apparent distribution volume is about 0.2 l/kg and the serum protein binding rate is approximately 25 %. Clavulanic acid passes through the placental barrier and traces of it can be found in breast milk.

Clavulanic acid is partly metabolised (approximately 50 – 70 %). About 40 % of the substance is eliminated through the kidneys (18 to 38 % of a dose in unchanged form). Total clearance is approximately 260 ml/min. The serum half-life in subjects with normal renal function is approximately 1 hour, in patients with creatinine clearance ranging between 20 and 70 ml/min it is approximately 2.6 hours and in anuria it ranges between 3 and 4 hours. After a single oral dose of 500/125 mg amoxicillin/clavulanic acid the average minimal plasma concentration (after 8 hours) of clavulanic acid was 0.08 mg/l. Clavulanic acid can be eliminated by means of haemodialysis.

Pharmacokinetically relevant interactions between amoxicillin and clavulanic acid have not been observed to date.

5.3 Preclinical safety data

The combination of amoxicillin and clavulanic acid is relatively well tolerated. Solely after very high doses (corresponding to 20- to 50-fold the maximum human dose) were reversible haematological and blood-chemical changes evident.

In vitro and *in vivo* studies did not reveal any signs of mutagenic effect.

There are no long-term animal experiments on tumour generating potential.

Studies in rats revealed that the combination of amoxicillin and clavulanic acid did not have any teratogenic effects. Tests on rats and mice for amoxicillin alone exhibited no effect on gravidity and no embryotoxic effects or deformities were detected. A pre/post-natal study with amoxicillin involving

rats showed the birth weight of exposed rats to be considerably lower compared to the control group. However, deformities and anomalies were not observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Povidone
Colloidal anhydrous silica
Magnesium stearate
Titanium dioxide
Basic butylated methacrylate copolymer
Talc
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Store below 25°C in the original packaging.
Protect from moisture and light.

6.5 Nature and contents of container

Aluminium/Aluminium blister.
Pack size: 16 film-coated tablets

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

Not applicable.

9. DATE OF FIRST AUTHORISATION IN GERMANY

Not applicable.

10. DATE OF REVISION OF THE TEXT

October 2018

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.