Summary Of Product Characteristics

1 Malmentin (Amoxicillin Sodium BP 1000mg and Clavulanic acid BP 200mg) Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 QUALITATIVE DECLARATION

Co-Amoxiclav for Injection BP 1.2 gm

2.2 QUANTITATIVE DECLARATION

Each vial conatins:

Sterile Amoxicillin Sodium BP

Equivalent to Amoxicillin……1000 mg

Sterile Potassium Clavulanate BP

Equivalent to Clavulanic Acid…….200 mg

3 Pharmaceutical Form

Powder for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

MALMENTIN should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

I.V. MALMENTIN 300mg (Paediatric)/ 600mg/ 1.2g is indicated for short-term treatment of bacterial infections at the following sites:

Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections e.g. acute exacerbation of chronic obstructive pulmonary disease (AECOPD)/acute exacerbation of chronic bronchitis (AECB), lobar and bronchopneumonia.

Genito-urinary tract infections e.g. cystitis, urethritis, pyelonephritis.

Skin and soft tissue infections e.g. boils, abscesses, cellulitis, wound infections.

Bone and joint infections e.g. osteomyelitis.

Other infections e.g. intra-abdominal sepsis.

I.V. MALMENTIN 300mg (Paediatric)/ 600mg/ 1.2g is also indicated for prophylaxis against infection which may be associated with major surgical procedures such as gastrointestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract.

Susceptibility to *MALMENTIN* will vary with geography and time (see *5. Pharmacological Properties, Pharmacodynamic Properties* for further information). Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

Infections caused by amoxycillin-susceptible organisms are amenable to *MALMENTIN* treatment due to its amoxycillin content. Mixed infections caused by amoxycillin-susceptible organisms in conjunction with *MALMENTIN*-susceptible β-lactamase producing organisms may therefore be treated with *MALMENTIN*.

4.2 Posology and Method of Administration

Dosage for the treatment of infections

Adults and children over 12 years	Usually 1.2 g eight hourly. In more serious infections, increase frequency to six-hourly intervals.
Children 3 months-12 years	Usually 30 mg/kg* *MALMENTIN* eight hourly. In more serious infections, increase frequency to six-hourly intervals.
Children 0-3 months	30 mg/kg* *MALMENTIN* every 12 hours in premature infants and in full term infants during the perinatal period, increasing to eight hours thereafter.

* Each 30 mg *I.V. MALMENTIN* contains 25 mg amoxycillin and 5 mg clavulanate.

Adult dosage for surgical prophylaxis

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

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

Dosage in Renal Impairment

Adults

Mild impairment (creatinine clearance >30 ml/min)	Moderate impairment (creatinine clearance 10-30 ml/min)	Severe impairment (creatinine clearance <10 ml/min)
No change in dosage	1.2 g IV stat, followed by 600 mg IV 12 hourly	1.2 g IV stat, followed by 600 mg IV 24 hourly. Dialysis decreases serum concentrations of *MALMENTIN* and an additional 600 mg IV dose may need to be given during dialysis and at the end of dialysis

Children

Similar reductions in dosage should be made for children.

Dosage in Hepatic Impairment

Administer with caution; monitor hepatic function at regular intervals.

Administration

I.V. MALMENTIN 600 mg/1.2 g may be administered either by intravenous injection or by intermittent infusion. *I.V. MALMENTIN 600 mg/ 1.2 g* is not suitable for intramuscular administration.

I.V. MALMENTIN 300 mg (Paediatric) should be administered only by intravenous injection. It is not suitable for intermittent infusion or intramuscular administration.

4.3 Contraindications

MALMENTIN is contraindicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.

MALMENTIN is contraindicated in patients with a previous history of *MALMENTIN*-associated jaundice/hepatic dysfunction.

4.4 Special Warnings and Precautions for Use

Before initiating therapy with *MALMENTIN*, careful enquiry should be made concerning previous hypersensitivity reactions, cephalosporins, or other allergens.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see *4.3 Contraindications*). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such

reactions can include chest pain occurring in association with an allergic reaction to *MALMENTIN* (see *4.8 Undesirable Effects)*. Drug-induced enterocolitis syndrome has been reported mainly in children receiving *MALMENTIN* (see *4.8 Undesirable Effects*). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. If an allergic reaction occurs, *MALMENTIN* therapy must be discontinued and appropriate alternative therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management (including intubation) may also be required.

Changes in liver function tests have been observed in some patients receiving *MALMENTIN*. The clinical significance of these changes is uncertain but *MALMENTIN* should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment *MALMENTIN* dosage should be adjusted as recommended in *4.2 Posology and Method of Administration* section.

MALMENTIN 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 amoxycillin.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further**.**

Abnormal prolongation of prothrombin time [increased International Normalized Ratio (INR)] has been reported rarely in patients receiving *MALMENTIN* and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

If the parenteral administration of high doses is necessary, the sodium content must be taken into account in patients on a sodium restricted diet.

In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy. During administration of high doses of amoxycillin it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxycillin crystalluria (see *4.9 Overdose*).

The presence of clavulanic acid in *MALMENTIN* may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

4.5 Drug Interactions

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxycillin. Concomitant use with *MALMENTIN* may result in increased and prolonged blood levels of amoxycillin but not of clavulanate.

Concomitant use of allopurinol during treatment with amoxycillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of *MALMENTIN* and allopurinol.

In common with other antibiotics, *MALMENTIN* may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

The presence of clavulanic acid in *MALMENTIN* may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

In the literature there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxycillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of *MALMENTIN*.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxycillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

4.6 Use in Special Populations

Pregnancy

Reproduction studies in animals (mice and rats) with orally and parenterally administered *MALMENTIN* have shown no teratogenic effects. In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with *MALMENTIN* may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, especially during the first trimester, unless considered essential by the physician.

Lactation

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

4.7 Effects on Ability to Drive and Use Machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable Effects

Data from large clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1000 and < 1/100
Rare ≥ 1/10,000 and < 1/1000
Very rare < 1/10,000

Infections and infestations

Common	Mucocutaneous candidiasis

Blood and lymphatic system disorders

Rare	Reversible leucopenia (including neutropenia) and thrombocytopenia
Very rare	Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time

Immune system disorders

Very rare	Angioneurotic oedema, anaphylaxis (see *4.4 Special Warnings and Precautions for Use*), serum sickness-like syndrome, hypersensitivity vasculitis (see also *Skin and subcutaneous tissue disorders*).

Nervous system disorders

Uncommon	Dizziness, headache
Very rare	Aseptic meningitis, convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Cardiac disorders

Very Rare	Kounis syndrome (see *4.4 Special Warnings and Precautions for Use*).

Vascular disorders

Rare	Thrombophlebitis at the site of injection

Gastrointestinal disorders

Common	Diarrhoea

Uncommon	Nausea, vomiting, indigestion
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis see *4.4 Special Warnings and Precautions for Use*) are less likely to occur after parenteral administration. Drug-induced enterocolitis syndrome (see *4.4 Special Warnings and Precautions for Use*)

Hepatobiliary disorders

Uncommon	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.
Very rare	Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

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.

Skin and subcutaneous tissue disorders

Uncommon	Skin rash, pruritus, urticaria
Rare	Erythema multiforme
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) (see also *Immune system disorders*). If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Linear IgA disease

Renal and urinary disorders

Very rare	Interstitial nephritis, crystalluria (see *4.9 Overdose*)

4.9 Overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Gastrointestinal symptoms may be treated symptomatically with attention to the water electrolyte balance.

Amoxycillin crystalluria, in some cases leading to renal failure, has been observed (see *4.4 Special Warnings and Precautions for Use*).

MALMENTIN can be removed from the circulation by haemodialysis.

Amoxycillin has been reported to precipitate in bladder catheters after intravenous administration of large doses. A regular check of patency should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Amoxycillin is a semisynthetic antibiotic with a broad spectrum of antibacterial activity against many gram-positive and gram-negative micro-organisms. Amoxycillin is, however, susceptible to degradation by beta-lactamases and therefore the spectrum of activity of amoxycillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in micro-organisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance. It is generally less effective against chromosomally-mediated type 1 beta-lactamases.

The presence of clavulanic acid in amoxycillin-clavulanate formulations protects amoxycillin from degradation by beta-lactamase enzymes and effectively extends the antibacterial spectrum of amoxycillin to include many bacteria normally resistant to amoxycillin and other penicillins and cephalosporins. Thus amoxycillin-clavulanate possesses the distinctive properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

Pharmacodynamic Properties

ATC Code: J01CR02
Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in *MALMENTIN* anticipates this defence mechanism by blocking the ß-lactamase enzymes, thus rendering the organisms susceptible to amoxycillin's rapid bactericidal effect at concentrations readily attainable in the body.

Clavulanate by itself has little antibacterial activity; however, in association with amoxycillin as *MALMENTIN,* it produces an antibiotic agent of broad spectrum with wide application in hospital and general practice.

In the list below, organisms are categorised according to their in *vitro* susceptibility to *MALMENTIN*.

In vitro* susceptibility of micro-organisms to *MALMENTIN

Where clinical efficacy of *MALMENTIN* has been demonstrated in clinical trials this is indicated with an asterisk (*).

Organisms that do not produce beta-lactamase are identified (with †). If an isolate is susceptible to amoxycillin, it can be considered susceptible to *MALMENTIN*.

Commonly susceptible species

Gram-positive aerobes:
Bacillius anthracis
Enterococcus faecalis
Gardnerella vaginalis
Listeria monocytogenes
Nocardia asteroides
*Streptococcus pneumoniae**†
*Streptococcus pyogenes**†
*Streptococcus agalactiae**†
Viridans group streptococcus†
Streptococcus spp. (other β-hemolytic)*†
Staphylococcus aureus (methicillin susceptible)*
Staphylococcus saprophyticus (methicillin susceptible)
Coagulase negative staphylococcus (methicillin susceptible)

Gram-negative aerobes:
Bordetella pertussis
*Haemophilus influenzae**
Haemophilus parainfluenzae
Helicobacter pylori
*Moraxella catarrhalis**
Neisseria gonorrhoeae
Pasteurella multocida
Vibrio cholerae

Other:
Borrelia burgdorferi
Leptospira ictterohaemorrhagiae
Treponema pallidum

Gram positive anaerobes:
Clostridium spp.
Peptococcus niger
Peptostreptococcus magnus
Peptostreptococcus micros
Peptostreptococcus spp.

Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides spp.
Capnocytophaga spp.
Eikenella corrodens
Fusobacterium nucleatum
Fusobacterium spp.

Porphyromonas spp. *Prevotella* spp.
Species for which acquired resistance may be a problem
Gram-negative aerobes: *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Klebsiella* spp. *Proteus mirabilis* *Proteus vulgaris* *Proteus* spp. *Salmonella* spp. *Shigella* spp.
Gram-positive aerobes: *Corynebacterium* spp. *Enterococcus faecium*
Inherently resistant organisms
Gram-negative aerobes: *Acinetobacter* spp. *Citrobacter freundii* *Enterobacter* spp. *Hafnia alvei* *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* spp. *Serratia* spp. *Stenotrophomas maltophilia* *Yersinia enterolitica*
Others: *Chlamydia pneumoniae* *Chlamydia psittaci* *Chlamydia* spp. *Coxiella burnetti* *Mycoplasma* spp.

5.2 Pharmacokinetic Properties

The pharmacokinetics of the two components of *MALMENTIN* are closely matched. Both clavulanate and amoxycillin have low levels of serum binding; about 70% remains free in the serum.

Doubling the dosage of *MALMENTIN* approximately doubles the serum levels achieved.

5.3 Animal Toxicology and Pharmacology

No further information of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENT(S)

None

6.2 INCOMPATIBILITIES

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

Co-Amoxiclav Injection should not be mixed with infusions containing glucose, dextran or bicarbonate.

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

6.3 SHELF-LIFE

24 MONTHS

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light

KEEP OUT OF REACH AND SIGHT OF CHILDREN

6.5 NATURE AND CONTENTS OF CONTAINER

20 ml plain glass vial packed with two FFS Ampoules of 10 ml Sterilized Water for Injection in a plastic tray along with an insert in a carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

For single use. Discard any unused contents.

7.0 APPLICANT/MANUFACTURER

Manufactured By:

SWISS PARENTERALS LIMITED (UNIT II)

Manufacturing site: Plot No 402,412-414, Kerala Industrial Estate,

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