FUGENTIN®

Broad Spectrum Antibiotic

Fugentin® Film coated tablets (875+125)mg/tab: White-off white, oblong, biconvex tablets scored on one side in blister packs of 4 tablets. Packs of 12 tablets.

Composition

Active Ingredients: Amoxicillin Trihydrate and Clavulanate Potassium.

Excipients: Magnesium stearate, silicon dioxide colloidal, sodium starch glycollate, cellulose microcrystalline, talc, titanium dioxide E171, hypromellose, diethylphthalate, dimeticone.

Pharmacology

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBP) 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 prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. According to the demands, 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 is resistant to penicillin should not be treated with this preparation of amoxicillin/clavulanic acid

[2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

Indications

Fugentin® is indicated for the treatment of the following infections in adults and children:

- 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.

Recommended Dosage

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 **Fugentin®** that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

The use of alternative presentations of **Fugentin®** (e.g. those that provide higher doses of amoxicillin or/and different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

For adults and children ≥40 kg, this formulation of **Fugentin®** provides a total daily dose of 1750 mg amoxicillin/250 mg clavulanic acid, when administered twice a day and 2625mg amoxicillin/375mg clavulanic acid acid when administered three times a day as recommended below. For children < 40 kg, this formulation of **Fugentin®** 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 **Fugentin®** is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

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.

Adults and children ≥40 kg

Recommended doses:

- Normal dose (for all indications) 875mg/125mg twice a day.
- Higher dose- (in particular for infections such as otitis media, sinusitis, lower respiratory and genitourinary tract infections): 875mg/125mg three times a day.

Children < 40 kg

Recommended doses:

- 25mg/3.6mg/kg/daily to 45mg/6.4mg/kg/daily given in two equally divided doses
- To 70mg/10mg/kg/daily in two equally divided doses may administered in some infections (such otitis media, sinusitis and lower tract infections).

No clinical data are available on doses of **Fugentin®** 7:1 formulations higher than 45 mg/6.4 mg/kg per day in children under 2 years.

No clinical data are available on **Fugentin®** 7:1 formulations in patients of age under 2 months. Dosage recommendations cannot be done for that population.

Elderly

No dose adjustment is considered necessary.

Renal impairment

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

In patients with creatine clearance lower than 30ml/min, the use of **Fugentin®** preparations with ratio amoxicillin to clavulanic acid 7:1 is not recommended , since adjustment in dose is not possible.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals.

Administration

Fugentin® 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 the SPC of the IV-formulation and continued with an oral preparation.

Side 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 **Fugentin®** are sorted by MedDRA System Organ Class and are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥1/10), Common (≥1/100 and <1/10), Uncommon (≥1/1,000 and <1/100), Rare (≥1/10,000 and <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not Known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not Known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT	Uncommon
Hepatitis	Not known
Cholestatic jaundice	Not known
Kin and subcutaneous tissue disorders	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria	Not known

Contra-Indications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

Use in Pregnancy and Lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, foetal development, labour or postnatal development. 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 premature labour 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.

Lactation

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.

Drug Interactions

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.

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.

Storage conditions

Fugentin® film coated tablets should be stored in temperature below 25°C, in a dry place.

Date of last revision of the text: 25-5-2010

ELPEN

ELPEN Pharmaceutical Co, Inc., Pikermi Attika – Greece