SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM:

[PRODUCT NAME] BD S (Powder for suspension)

[PRODUCT NAME] BD SF (Powder for suspension)

COMPOSITION:

- **[PRODUCT NAME] BD S** (Powder for suspension):

  when reconstituted according to instructions each 5 ml contains amoxicillin trihydrate equivalent to 200 mg amoxicillin and potassium clavulanate equivalent to 28,5 mg clavulanic acid.

- **[PRODUCT NAME] BD SF** (Powder for suspension):

  when reconstituted according to instructions each 5 ml contains amoxicillin trihydrate equivalent to 400 mg amoxicillin and potassium clavulanate equivalent to 57,0 mg clavulanic acid.

Excipients:

- Colloidal silicon dioxide (Aerosil 200), hydroxpropylmethylcellulose, (Metosel E-3(3 cps)), methyl paraben, orange flavour, silicon dioxide (Syloid AL-1-FP), sodium saccharin, succinic acid, golden syrup flavour, xanthan gum.

  Contains saccharin sodium as sweetener and methyl paraben 0,5 % *m/m* as preservative.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

[PRODUCT NAME] is the group name for the formulations containing a broad spectrum penicillin, amoxicillin and potassium clavulanate. Potassium clavulanate has been shown *in vitro* to be an irreversible inhibitor of beta-lactamases. Potassium clavulanate however does not inactivate the chromosomally mediated (Sykes Type 1 Cephalosporinase) beta-lactamases produced by *Acinetobacter* species, *Citrobacter* species, *Enterobacter*, Indole positive *Proteus, Providencia* species and *Serratia marcescens*. *In vitro* the **[PRODUCT NAME]** formulation shows synergism against amoxicillin-resistant organisms, with no evidence of antagonism and the activity is not reduced in the presence of serum. (*In vitro* activity does not necessarily imply *in vivo* efficacy).

The amoxicillin component of the formulations exerts a bactericidal action against many strains of Gram-positive and Gram-negative organisms. The clavulanic acid component has very little bactericidal action. It does however, by inactivation of susceptible beta-lactamases, protect amoxicillin from degradation by a large number of beta-lactamase enzymes produced by penicillin resistant strains of organisms.

Organisms inherently resistant against the amoxicillin and clavulanic acid combination may include:

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

Pharmacokinetic properties:

Absorption:

Both components, amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH and are well absorbed when taken orally. Absorption is optimised when taken at the start of a meal.

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1-2 hours after administration.

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither are adversely affected by the presence of food in the stomach.

Distribution:

Approximately 17 - 20 % of the total plasma amoxicillin content is protein bound. Clavulanic acid is approximately 25 % protein bound. Amoxicillin diffuses readily into most body tissues with the exception of the brain and spinal fluid. Inflammation generally increases the permeability of the meninges to penicillins and this may apply to amoxicillin.

Excretion:

The major route of elimination is via the kidneys for amoxicillin whilst for clavulanic acid it is by both renal and non-renal mechanisms. Approximately 60 – 70 % of amoxicillin and 40 – 65 % of clavulanic acid are excreted unchanged in the urine in the first 6 hours after an oral dose. Amoxicillin is partly excreted in the urine as the inactive metabolite penicilloic acid. Clavulanic

acid is extensively metabolised and the metabolites are eliminated via urine and faeces. Co-administration of probenecid delays amoxicillin excretion, but has little effect on the excretion of the clavulanic acid component of the formulation. Small amounts of amoxicillin are also excreted in the faeces and bile.

The elimination pharmacokinetics seen in adults also apply to children with mature kidney function.

INDICATIONS:

[PRODUCT NAME] is indicated for the treatment of infections caused by amoxicillin-resistant organisms producing beta-lactamases sensitive to clavulanic acid, in the following infections:

- Upper respiratory tract infections, such as sinusitis, otitis media, or recurrent tonsillitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pyogenes* sensitive to **[PRODUCT NAME].**
- Lower respiratory tract infections, such as acute exacerbations of chronic bronchitis and bronchopneumonia caused by *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis* sensitive to **[PRODUCT NAME]**.
- Genito-urinary tract infections, such as cystitis, urethritis, pyelonephritis, caused by *Enterobacteriaceae* (mainly *Escherichia coli*), *Staphylococcus saprophyticus* and *Enterococcus* species sensitive to **[PRODUCT NAME]**.
- Skin and soft tissue infections caused by methicillin susceptible *Staphylococcus aureus, Streptococcus pyogenes* and *Bacteroides* species.

[PRODUCT NAME] will also be effective in the treatment of infections caused by amoxicillin-sensitive organisms at the appropriate amoxicillin dosage since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

CONTRAINDICATIONS:

- Previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction.

- Hypersensitivity to amoxicillin, clavulanic acid, other penicillins, cephalosporins, or any other ingredient of [PRODUCT NAME]. Cross-sensitivity between penicillins and cephalosporins is well documented.
- Safety in children under 2 months of age has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

- Serious and occasionally fatal hypersensitivity reactions including anaphylaxis have been reported in patients on penicillin therapy. Before initiating therapy with **[PRODUCT NAME]**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillin. Hypersensitivity reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins.

  If an allergic reaction occurs, **[PRODUCT NAME]** should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with epinephrine (adrenaline).
- **[PRODUCT NAME]** contains amoxicillin, an aminopenicillin, it is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of morbiliform rash if amoxicillin is used.
- Prolonged use may result in overgrowth of non-susceptible organisms such as *Clostridium difficile* and *Candida*.

  The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter, Pseudomonas,*

Clostridium difficile or Candida), **[PRODUCT NAME]** should be discontinued and/or appropriate therapy instituted.

- Pseudomembranous enterocolitis may occur.
- Abnormal prolongation of prothrombin time (increased INR) has been reported in patients receiving amoxicillin-clavulanic acid concomitantly with oral anticoagulants, e.g. warfarin. Appropriate monitoring should be undertaken with the addition or withdrawal of **[PRODUCT NAME].**
- 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.
- Use of **[PRODUCT NAME]** may lead to the selection of resistant strains of organisms and sensitivity testing should be carried out whenever possible.
- **[PRODUCT NAME]** should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.
- Periodic assessment of organ function, including renal, hepatic and haematopoietic functions, is advisable during prolonged therapy.

***Impaired hepatic function*:**

- Transient hepatitis and cholestatic jaundice may occur.

Changes in liver function tests may occur. It should be used with care in patients with evidence of severe hepatic dysfunction. Hepatic function should be monitored regularly (see **DOSAGE AND DIRECTIONS FOR USE**).

***Impaired renal function*:**

- In patients with moderate or severe renal impairment **[PRODUCT NAME]** dosage should be adjusted (see **DOSAGE AND DIRECTIONS FOR USE**).

Effects on the ability to drive and use machines

Patients should establish the effects of **[PRODUCT NAME]** on their individual ability to drive and use machines before they perform such actions.

INTERACTIONS:

- Concurrent use of **[PRODUCT NAME]** with probenecid is not recommended since probenecid decreases the renal tubular secretion of amoxicillin, but does not affect clavulanic acid excretion resulting in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.
- **[PRODUCT NAME]** may reduce the efficacy of combined oral contraceptives. Patients should be warned accordingly.
- The concomitant administration of allopurinol and amoxicillin-clavulanic acid can substantially increase the incidence of skin rashes as compared to patients receiving amoxicillin-clavulanic acid alone.
- Tetracyclines and other bacteriostatic medicines may interfere with the bactericidal effects of amoxicillin.
- The ingestion of alcohol and **[PRODUCT NAME]** may precipitate a disulfiram like reaction. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with **[PRODUCT NAME].**

Interactions with laboratory tests:

- During treatment with **[PRODUCT NAME]** false positive readings may occur with chemical methods to test for glucose in the urine. Enzymatic glucose oxidase methods should be used.

PREGNANCY AND LACTATION:

Pregnancy:

- The safety of **[PRODUCT NAME]** in pregnancy and lactation has not been established.

- In women with pre-term premature rupture of the foetal membrane (PROM), it was reported that prophylactic treatment with amoxicillin-clavulanate may be associated with an increased risk of necrotising enterocolitis in neonates.

Lactation:

- Amoxicillin is excreted in breast milk. There is no data on the excretion of clavulanate in breast milk. The use of **[PRODUCT NAME]** by nursing mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant.

DOSAGE AND DIRECTIONS FOR USE:

Dosage:

- **[PRODUCT NAME]** should be taken immediately before a meal.
- Shake the bottle well before each dose.
- The duration of treatment should be appropriate to the indication and should not exceed 14 days without review.
- **[PRODUCT NAME] BD S:** For reconstitution to 70 ml: water is required to be added up to the marked line indicated on the bottle. Shake the bottle first to loosen the powder, add water to half of the mark, invert bottle and shake well until the powder is dispersed. Add water to bring the level to the mark on the bottle. Shake well.

[PRODUCT NAME] BD SF: For reconstitution to 70 ml: water is required to be added up to the marked line indicated on the bottle. Shake the bottle first to loosen the powder, add water to half of the mark, invert bottle and shake well until the powder is dispersed. Add water to bring the level to the mark on the bottle. Shake well.

For reconstitution to 35 ml: water is required to be added up to the marked line indicated on the bottle. Shake the bottle first to loosen the powder, add water to half of the mark, invert bottle and shake well until the powder is dispersed. Add water to bring the level to the mark on the bottle. Shake well.

Dosages:

General Information:

- For infections caused by amoxicillin-sensitive organisms the dosage is that approved for amoxicillin as the clavulanic acid component does not contribute to the therapeutic effect.
- Dosage depends on the age, weight and renal function of the patient and the severity of the infection.

Children 2 – 12 years:

- The dose of **[PRODUCT NAME] BD** in children is 28,6 – 51,4 mg/kg/day which corresponds to a daily dosage of the equivalent of 25 – 45 mg/kg of amoxicillin and 3,6 – 6,4 mg/kg of clavulanic acid, to be taken in divided doses every twelve hours, at the start of a meal.
- The dose of **[PRODUCT NAME] BD** in children is 28,6 – 51,4 mg/kg/day which corresponds to a daily dosage of the equivalent of 25 – 45 mg/kg of amoxicillin and 3,6 – 6,4 mg/kg of clavulanic acid, to be taken in divided doses every twelve hours, at the start of a meal.

Directions for use	In divided doses, twice daily (every 12 hours), at the start of a meal.
Lower dose (mg/kg/day)	25/3,6 – 45/6,4
Higher dose (mg/kg/day)	45/6,4 – 70/10

- The lower dose is recommended for infections such as skin and soft tissue and recurrent tonsillitis.
- The higher dose is recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections.
- Children weighing 40 kg and over should be dosed according to adult recommendations.

AMOXICILLIN-SENSITIVE ORGANISMS

PRODUCT	**UPPER RESPIRATORY TRACT INFECTIONS**	**LOWER RESPIRATORY TRACT INFECTIONS**	**URINARY TRACT INFECTIONS**	**SKIN and SOFT TISSUE INFECTIONS**

[PRODUCT NAME] BD S 13 – 21 kg (2 – 6 years)	2,5 – 5 ml[(1)] 12 hourly	2,5 – 5 ml[(1)] 12 hourly	2,5 – 5 ml[(1)] 12 hourly	2,5 – 5 ml[(1)] 12 hourly
[PRODUCT NAME] BD SF 22 – 40 kg (7 – 12 years)	5 – 10 ml[(2)] 12 hourly	5 – 10 ml[(2)] 12 hourly	5 – 10 ml[(2)] 12 hourly	5 – 10 ml[(2)] 12 hourly

AMOXICILLIN-RESISTANT ORGANISMS

PRODUCT	**UPPER RESPIRATORY TRACT INFECTIONS** **(otitis media)** ***H. influenza***	**LOWER RESPIRATORY TRACT INFECTIONS** **(bronchitis)** ***H.influenzae***	**URINARY TRACT INFECTIONS** ***E.coli*** ***Klebsiella pneumonia***	**SKIN & SOFT TISSUE INFECTIONS** ***Methicillin sensitive*** ***Staphylococcus aureus***
[PRODUCT NAME] BD S 13 – 21 kg (2 – 6 years)	2,5 – 5 ml[(1)] 12 hourly	2,5 – 5 ml[(1)] 12 hourly	2,5 – 5 ml[(1)] 12 hourly	2,5 – 5 ml[(1)] 12 hourly
[PRODUCT NAME] BD SF 22 – 40 kg (7 – 12 years)	5 – 10 ml[(2)] 12 hourly	5 – 10 ml[(2)] 12 hourly	5 – 10 ml[(2)] 12 hourly	5 – 10 ml[(2)] 12 hourly

[(1)] To correspond to a dosage of 28, 6 mg/kg/day.

[(2)] To correspond to a dosage of 51, 4 mg/kg/day.

Children aged 2 months to 2 years:

- Children under 2 years should be dosed according to body weight.
- **[PRODUCT NAME]** suspensions are contraindicated in children under 2 months of age.

Impaired renal function:

Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each, but particularly of amoxicillin, increases in patients with renal failure. Therefore, the dose may need to be reduced or the interval extended. Dosage adjustments are based on the maximum recommended level of amoxicillin.

The following schedule is proposed:

creatinine clearance greater than 30 ml/minute	**creatinine clearance 10 to 30 ml/minute**	**creatinine clearance less than 10 ml/minute**
No change in dosage	15/3,75 mg/kg given 12 hourly. Maximum amoxicillin dose: 30 mg/kg/day	15/3,75 mg/kg given as a single daily dose. Maximum amoxicillin dose: 15 mg/kg/day.

[PRODUCT NAME] suspensions are NOT recommended for children with a creatinine clearance of less than 30 ml/minute.

No dosage recommendations can be made for premature infants since

[PRODUCT NAME] is not recommended for children under 2 months of age.

Haemodialysis decreases serum concentrations of both amoxicillin and clavulanic acid and additional doses should be administered at the end of dialysis.

SIDE EFFECTS

The incidence and severity of adverse effects, particularly nausea and diarrhoea, can be minimised by administering **[PRODUCT NAME]** at the start of a meal.

The following adverse reactions may occur with **[PRODUCT NAME]:**

Infections and infestations:

Frequent: Mucocutaneous candidiasis (including vaginitis)

Blood and lymphatic system disorders:

Less frequent: Haemolytic anaemia, reversible thrombocytopenia, reversible leucopenia (including neutropenia), reversible agranulocytosis and prolongation of prothrombin and bleeding time (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Monitor appropriately when anticoagulants are concomitantly prescribed.

Immune system disorders:

Less frequent: Angioedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis.

Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Nervous system disorders:

Less frequent: Dizziness, headache, reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting. Nausea is more common with higher oral doses.

Less frequent: Indigestion, abdominal pain and abnormal taste, gastritis, stomatitis, glossitis, black “hairy” tongue, enterocolitis and antibiotic-associated colitis (including pseudomembranous colitis, Clostridium difficile-associated diarrhoea (CDAD) and haemorrhagic colitis). Superficial tooth discolouration can occur which can be removed by brushing.

If gastro-intestinal reactions are evident, they may be reduced by taking **[PRODUCT NAME]** at the start of a meal.

Hepato-biliary disorders:

Less frequent: Hepatitis and cholestatic jaundice, a moderate rise in AST and/or ALT.

Hepatic events may be severe and fatal and may be associated with prolonged treatment. Signs and symptoms may occur shortly after treatment, but in some cases may not become apparent until become apparent several weeks after treatment has ceased.

Skin and subcutaneous tissue disorders:

Less frequent: Skin rashes, pruritus and urticaria, erythema multiforme, Stevens-Johnson syndrome, hypersensitivity, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and toxic epidermal necrolysis.

Whenever such reactions occur, **[PRODUCT NAME]** should be discontinued.

Renal and urinary disorders:

Less frequent: Interstitial nephritis, crystalluria. (see **WARNINGS AND SPECIAL PRECAUTIONS AND KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENTS)**

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS:

- Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.
- Adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria which in some cases can lead to renal failure.
- **[PRODUCT NAME]** may be removed from circulation by haemodialysis, and clavulanic acid may also be removed by haemodialysis.

IDENTIFICATION:

- **[PRODUCT NAME] BD S 70 ml** (Powder for suspension)**:**

Before reconstitution: White to cream coloured, orange – golden syrup odoured, homogeneous powder mixture.

After reconstitution: When diluted according to label white to cream coloured homogeneous suspension with aromatic odour (orange-golden syrup).

- **[PRODUCT NAME] BD SF 35 ml** (Powder for suspension)**:**

Before reconstitution: White to cream coloured, orange – golden syrup odoured, homogeneous powder mixture.

After reconstitution: When diluted according to label white to cream coloured homogeneous suspension with aromatic odour (orange-golden syrup).

- **[PRODUCT NAME] BD SF 70 ml** (Powder for suspension)**:**

Before reconstitution: White to cream coloured, orange – golden syrup odoured, homogeneous powder mixture.

PRESENTATION:

- **[PRODUCT NAME] BD S 70 ml** (Powder for suspension)**:**

  is packed in a Type III amber coloured, 100 ml glass bottle (marked to 70 ml), with a 31 PP neck that is closed with a white polypropylene cap with a safety strap. The bottle and transparent spoon (marked to 1,25 ml; 2,5 ml and 5 ml) are placed together with a patient information leaflet in a carton box.

- **[PRODUCT NAME] BD SF 35 ml** (Powder for suspension forte)**:**

  is packed in a Type III amber coloured, 100 ml glass bottle (marked to 35 ml), with a 31 PP neck that is closed with a white polypropylene cap with a safety strap. The bottle and 4,5 ml pipette are placed together with a patient information leaflet in a carton box.

- **[PRODUCT NAME] BD SF 70 ml** (Powder for suspension forte)**:**

  is packed in a Type III amber coloured, 100 ml glass bottle (marked to 70 ml), with a 31 PP neck that is closed with a white polypropylene cap with a safety strap. The bottle and transparent spoon (marked to 1,25 ml; 2,5 ml and 5 ml) are placed together with a patient information leaflet in a carton box.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep tightly closed.

After reconstitution, store the suspension in a refrigerator between 2 °C and 8 °C and use within 7 days. Do not freeze.

Store in the original packaging until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

CO AMOXICLAV BD S AUSTELL : 48/20.1.2/1175

CO AMOXICLAV BD SF AUSTELL : 48/20.1.2/1176

AVUTAN BD S : 48/20.1.2/1177

AVUTAN BD SF : 48/20.1.2/1178

CO AMOXICLAV BD S APEX : 48/20.1.2/1179

CO AMOXICLAV BD SF APEX 48/20.1.2/1180

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION.

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DATE OF PUBLICATION OF THE PACKGE INSERT:

Date on the registration certificate: 25 November 2016