SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MOXICLAV BIS 457mg/5ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Moxiclav Bis contains 400 mg amoxicillin and 57 mg clavulanic acid per 5ml (co-amoxiclav 400/57). The amoxicillin is present as amoxicillin trihydrate and the clavulanic acid is present as potassium clavulanate.

Excipient with known effect: sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension.
A white to off-white dry powder for reconstitution in water to form a white to off-white suspension with characteristic odour .

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Moxiclav Bis should be used in accordance with local official antibiotic prescribing guidelines and local susceptibility data.

Moxiclav Bis suspension for twice daily oral dosing, is indicated for short term treatment of bacterial infections at the following sites when amoxicillin resistant beta-lactamase producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.

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

Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia.

Urinary tract infections e.g. cystitis, urethritis, pyelonephritis.

Skin and soft tissue infections e.g. cellulitis, animal bites.

Susceptibility to Moxiclav Bis will vary with geography and time. Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Moxiclav Bis susceptible beta-lactamase producing organisms may be treated with Moxiclav Bis suspension 457 mg/5 ml. These infections should not require the addition of another antibiotic resistant to beta-lactamases.

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 Moxiclav Bis 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 Moxiclav (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).

The usual recommended daily dosage is:

• 25/3.6 mg/kg/day in mild to moderate infections (upper respiratory tract infections e.g. recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections).

• 45/6.4 mg/kg/day for the treatment of more serious infections (upper respiratory tract infections e.g. otitis media and sinusitis, lower respiratory tract infections e.g. bronchopneumonia and urinary tract infections).

No clinical data are available on doses above 45/6.4 mg/kg/day in children under 2 years.

There are no clinical data for Moxiclav Bis suspension 457 mg/5 mL to make dosage recommendations for children under 2 months old.

The tables below give dosage guidance for children.

25/3.6 mg/kg/day	2 - 6 years (13 - 21 kg)	2.5 ml Moxiclav Bis suspension 457 mg/5 mL twice daily.
	7 - 12 years (22 - 40 kg)	5.0 ml Moxiclav Bis suspension 457 mg/5 mL twice daily.

45/6.4 mg/kg/day	2 - 6 years (13 - 21 kg)	5.0 ml Moxiclav Bis suspension 457 mg/5 mL twice daily.
	7 - 12 years	10.0 ml Moxiclav Bis suspension 457 mg/5 ml twice daily.

Children aged 2 months to under 2 years

Children under 2 years should be dosed according to body weight.

Moxiclav Bis suspension 457 mg/5 mL		
Body Weight (kg)	*Lower dose at 25/3.6 mg/kg/day (mL every 12 hours)*	*Higher dose at 45/6.4 mg/kg/day (mL every 12 hours)*
2	*0.3*	*0.6*
3	*0.5*	*0.8*
4	*0.6*	*1.1*
5	*0.8*	*1.4*
6	*0.9*	*1.7*
7	*1.1*	*2.0*
8	*1.3*	*2.3*
9	*1.4*	*2.5*
10	*1.6*	*2.8*
11	*1.7*	*3.1*
12	*1.9*	*3.4*
13	*2.0*	*3.7*
14	*2.2*	*3.9*
15	*2.3*	*4.2*

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 Moxiclav Bis 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). There is, as yet, insufficient evidence on which to base a dosage recommendation"

Method of administration

Moxiclav Bis is for oral use.

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

Treatment should not exceed 14 days without review.

Therapy can be started parenterally according to the SmPC of the IV-formulation and continued with an oral preparation.

Shake to loosen powder, add water as directed, invert and shake.

Shake the bottle before each dose (see section 6.6).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.
- *History of hypersensitivity to beta-lactams, e,g. cephalosporins*
- 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 (including anaphylactoid and severe cutaneous adverse reactions) 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. Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management (including intubation) may also be required.

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 Moxiclav Bis 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.

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 Moxiclav Bis 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).

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.

Pseudomembranous 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. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, Moxiclav Bis should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated 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, Moxiclav Bis is not recommended.

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 Moxiclav Bis 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.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

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.

Allopurinol

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of Moxiclav Bis and allopurinol.

Oral contraceptives

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

Mycophenolate Mofetil

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 amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

4.6 Fertility, pregnancy and lactation

Pregnancy

Reproduction studies in animals (mice and rats) with orally and parenterally administered amoxicillin/clavulanic acid have shown no teratogenic effects. 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

Moxiclav Bis 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

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with amoxicillin/clavulanic acid, sorted by MedDRA System Organ Class 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 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)

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[1]	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
Aseptic meningitis	Very rare
Reversible hyperactivity	Not known

Convulsions[2]	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Tooth discolouration[11]	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders [7]	
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)[9]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

[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 X 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.

4.9 Overdose

Symptoms and signs of overdose

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.

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)

Treatment of intoxication

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: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mode 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.

PK/PD 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.

In the list below, organisms are categorised according to their in vitro susceptibility to amoxicillin/clavulanic acid.

In vitro susceptibility of micro-organisms to amoxicillin/clavulanic acid Where clinical efficacy of amoxicillin/clavulanic acid 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 amoxicillin, it can be considered susceptible to amoxicillin/clavulanic acid
Commonly susceptible species

Gram-positive aerobes:
Bacillius anthracis
Enterococcus faecalis
Gardnerella vaginalis
Listeria monocytogenes
Streptococcus pneumoniae†*
Streptococcus pyogenes†*
Streptococcus agalactiae†*
Viridans group streptococcus†
Streptococcus spp. (other beta-hemolytic)†*
*Staphylococcus aureus (methicillin susceptible)**
Staphylococcus saprophyticus (methicillin susceptible)
Coagulase negative staphylococcus (methicillin susceptible)
Gram-negative aerobes:
Bordetella pertussis
*Haemophilus influenzae**
Helicobacter pylori
*Moraxella catarrhalis**
Neisseria gonorrhoeae
Pasteurella multocida
Vibrio cholerae
Gram-positive anaerobes:
Clostridium spp.
Peptococcus niger
Peptostreptococcus magnus
Peptostreptococcus micros
Peptostreptococcus spp.
Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides spp.
Fusobacterium nucleatum
Fusobacterium 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.

Infections caused by amoxicillin-susceptible organisms are amenable to Moxiclav Bis treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Moxiclav Bis-susceptible beta-lactamase producing organisms may therefore be treated with Moxiclav Bis

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 (T_{max}) 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 pharmacokinetic parameters					
Drug Administration	Dose	C_{max}	T_{max} *	AUC	T 1/2
	(mg)	(mg/L)	(hours)	(mg.h/L)	(hours)
Amoxicillin /Clavulanic acid 1g					
Amoxicillin	875	12.4	1.5	29.9	1.36
Clavulanate	125	3.3	1.3	6.88	0.92
* Median values					

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

Nonclinical 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 Moxiclav Bis or its components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Xanthan gum (E415),
- hypromellose E5 2910,
- saccharin sodium (E954),
- colloidal anhydrous silica,
- silicon dioxide (E551),
- strawberry flavor (maltodextrin, sucrose, propylene glycol (E1520), acetic acid (E260), modified maize starch (E1450))
- peach flavor (maltodextrin, propylene glycol (E1520), Arabic gum (E414)
- lemon flavor (maltodextrin, acacia (E414), ascorbic acid (E300))
- succinic acid (E363).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Reconstituted suspensions: 7 days when stored in a refrigerator (2-8 ^{o}C).

6.4 Special precautions for storage

Store below 25°C in the original package in order to protect from light and moisture.
For storage conditions after reconstitution, see section 6.3

6.5 Nature and contents of container

Brown semitransparent glass bottles, TYPE III (with aluminium white caps).
Bottles of 100 ml bottle size for 70 ml suspension.
Bottles of 200 ml bottle size for 140 ml suspension.
Each bottle is packed together with a CE-marked oral syringe made of polyethylene and polystyrene bearing a printed graduation scale on the dosing plunger ranging from 0.5 ml to 10 ml with 0.5 ml scale intervals.

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. Add volume of drinking water (as indicated below) invert and shake well. Alternatively fill the bottle with drinking water to just below the mark on bottle label, invert and shake well, then top up with drinking water exactly to the mark, invert and again shake well.

Strength	**Volume of drinking water to be added at reconstitution (ml)**	**Final volume of reconstituted oral suspension (ml)**
400 mg/57 mg/5 ml	60	70
	120	140

Shake the bottle well before each dose.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Medochemie Ltd (Factory B) - Oral Facility
48 Iapetou Street, Agios Athanassios Industrial Area, 4101 Agios Athanassios, Limassol, Cyprus

8. DATE OF REVISION OF THE TEXT

10/2021