1.3.1 Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Dioclav 625 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Amoxicillin Ph.Eur. Equivalent to anhydrous amoxicillin 500 mg Clavulanate Potassium equivalent to Clavulanic acid 125 mg.

Sr. No	Ingredients	Quantity / tablet in mg	Function
Active Ingredient			
1.	Amoxicillin trihydrate* (compacted)	589.83	Active ingredient
2.	Potassium Clavulanate ** + Microcrystalline cellulose (MCC) (1:1)	325.0	Active ingredient
Inactive Ingredients			
3.	Colloidal silicon dioxide	7.50	Glidant
4.	Microcrystalline cellulose (PH 112)	61.04	Filler
5.	Croscarmellose sodium	42.00	Disintegrant
6.	Butylated hydroxy toluene	5.120	Antioxidant
7.	Purified talc	21.00	Glidant
8.	Magnesium Stearate	13.50	Lubricant

PRODUCT: DIOCLAV 625 mg (Amoxicillin and Clavulanate Potassium Tablets)	*CONFIDENTIAL*

MODULE 1	REGIONAL ADMINISTRATIVE INFORMATION
SECTION	1.3 PRODUCT INFORMATION
SUB SECTION	1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Sr. No	Ingredients	Quantity / tablet in mg	Function
Film Coating Material $			
9.	Hydroxy propyl methyl Cellulose 15cps	23.400	Film forming polymer
10.	Hydroxy propyl methyl Cellulose 5cps	5.130	Film forming polymer
11.	Titanium dioxide	6.95	Opaquing agent
12.	Purified talc	3.08	Coating aid
13.	PEG 400	6.43	Plasticizer
14.	Purified water	q.s	Vehicle
15.	Isopropyl alcohol	q.s	Vehicle

* The given quantity is based on 98.0% assay on anhydrous basis and 13.5% water content. Calculate the actual quantity of amoxicillin per tablet by the formula:

$$\frac{500 \times 100 \times 100 \text{ mg}}{(\text{Assay on anhydrous basis}) \times (100 - \% \text{ water content})}$$

** The given quantity is based on 41.0 % assay and 1.5 % water content. Calculate the actual quantity of potassium clavulanate + microcrystalline cellulose (1:1) per tablet by the formula:

$$\frac{131.25 \times 100 \times 100}{(\text{Assay on anhydrous basis}) \times (100 - \% \text{ water content})}$$

** Includes 5 % overages.

$ The target coating weight build up is 3.0 %, the given quantities contains extra to compensate for processing losses..

3. PHARMACEUTICAL FORM

Off-white oval shaped biconvex, film coated tablets, with "607" embossed on one side and other side plain.

4. THERAPEUTIC INDICATIONS

Anti Bacterial

4.1 POSOLOGY AND METHOD OF ADMINISTRATION

Adults: The usual dose is one 500 mg tablets if amoxicillin/Clavulanate potassium every 12 hours or one 250 mg tablet of amoxicillin/Clavula nate potassium every 8 hours. For more sever infections and infections of the respiratory tract the dose should be 875 mg tablet of amoxicillin/Clavulanate potassium every 12 hours or one 500 mg tablet of amoxicillin/Clavulanate potassium every 8 hours.

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with glomerular filtration rate of <30ml/min should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 ml/min should receive 500 mg or 250 mg every 12 hours depending on the severity of the infection. Patients with a less than 10 ml/min glomerular filtration rate should receive 500 mg or 250 mg every 24 hours depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

Administration: Amoxicillin/Clavulanate potassium may be taken without regard to meals; however, absorption of Clavulanate potassium is enhanced when amoxicillin/Clavulanate potassium is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance; amoxicillin/Clavulanate potassium should be taken at the start of a meal.

Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

Route of administration: Oral

4.2 INDICATIONS

Dioclav tablets (Amoxicillin and Clavulanate Potassium tablets) are indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

- Lower respiratory tract infections caused - by β-lactamases producing strains of H.influenza and M.catarrhalis.
- Otitis Media caused by - β-lactamases producing strains of H.influenza and M.catarrhalis.
- Sinusitis- caused by β-lactamases producing strains of H.influenza and M.catarrhalis.
- Bone and joint infections (e.g. osteomyelitis)
- Skin and Skin structure infections – caused by β-lactamases producing strains of S.aureus, E.coli and Klebsiella spp.
- Genito-Urinary Tract infections – caused by lactamases producing strains of E.coli, Klebsiella spp and Enterobacter spp.
- Dental infections (e.g dentoalveolar)
- Other infections (eg. Septic abortion, puerperal abortions, intra-abdominal sepsis)

While Amoxicillin / Clavulanate potassium is indicated only for the conditions listed above, infections caused by ampicillin – susceptible organisms are also amenable to treatment with amoxicillin/Clavulanate potassium due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamases producing organisms susceptible to amoxicillin/Clavulanate potassium should not require the addition of another antibiotic. Because Amoxicillin has greater in vitro activity against Streptococcus pneumoniae than does ampicillin or penicillin, the majority of S.Pneumoniae strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and amoxicillin/Clavulanate potassium.

To reduce the development of drug resistant bacteria and maintain the effectiveness of amoxicillin and amoxicillin/clavulanate potassium and other antibacterial drugs, amoxicillin and amoxicillin/clavulanate potassium should be used only to treat or prevent infection that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Bacteriological studies, to determine their causative organisms and their susceptibility to amoxicillin/clavulanate potassium, should be performed together with any indicated surgical procedures.

4.3 PRECAUTIONS AND WARNINGS

Precautions

General

While amoxicillin/clavulanate possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Prescribing amoxicillin/clavulanate potassium in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Warnings

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATEINTS ON PENCILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVTY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENCILLIN HYPERSENSTIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AMOXICILLIN/CLAVULANATE POTASSIUM, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSTIVITY REACTIONS TO PENCILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN/CLAVULANTE POTASSIUM SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN,

INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATIONS SHOULD ALSO BE ADMINISTRED AS INDICATED.

Clostridium difficile associated diarrhea (CDAD) been reported with use of nearly all antibacterial agents, including amoxicillin/clavulanate potassium, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C.difficile

C.difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementations, antibiotic treatment of C. difficile and surgical evaluation should be instituted as clinically indicated.

Amoxicillin/clavulanate potassium should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications

4.4 DRUG INTERACTIONS:

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin/clavulanate potassium may result in increased and prolonged blood levels of amoxicillin. Co-administration of Probenecid cannot be recommended.

Abnormal prolongation of prothrombin time (increase international normalized [NR]) has been reported rarely in patients receiving amoxicillin 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.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with amoxicillin/clavulanate potassium and allopurinol administered concurrently.

In common with other broad-spectrum antibiotics, amoxicillin/clavulanate may reduce the efficacy of oral contraceptives.

Laboratory test Interactions

Oral administration of amoxicillin/clavulanate potassium will result in high urine concentrations of amoxicillin. High urine concentration of ampicillin may result in false – positive reactions when testing for the presence of glucose in urine using CLINITEST® Benedicts Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore amoxicillin/clavulanate potassium, it is recommended that glucose test based on enzymatic glucose oxidase reactions (such as CLINITEST®) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore amoxicillin/clavulanate potassium.

Carcinogenicity/Mutagenicity/Impairment of fertility

Carcinogenicity: Long-term studies in animals have not been performed to evaluate carcinogenic potential

Mutagenicity: The mutagenic potential of amoxicillin/clavulanate potassium was investigated in vitro with an Ames test, a human lymphocyte cytogenetic assay, a yeast test, and a mouse lymphoma forward mutation assay and in vivo with mouse micronucleus tests and a dominant lethal test. All were negative apart from the in vitro mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

Impairment of fertility: Amoxicillin/Clavulanate potassium at oral doses of up to 1,200 mg/kg/day (5.7 times the maximum adult human dose based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with 2:1 ratio formulation of amoxicillin: clavulanate.

Use In Children

Pediatric patients weighing 40kg or more should be dosed according to the adult recommendation. Safety and effectiveness of amoxicillin/Clavulanate potassium tablets in pediatric patients weighing less than 40kg have not been established.

4.5 PREGNANCY AND LACTATION

Reproduction studies performed in pregnant rats and mice given amoxicillin/Clavulanate potassium at oral dosages upto 1,200 mg/kg/day (4.9 and 2.8 times the maximum adult human oral dose based on body surface area, respectively), revealed no evidence of harm to the fetus due to amoxicillin/Clavulanate potassium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions; however, it is not known whether the use of amoxicillin/clavulanate potassium in humans during labor or delivery

has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with amoxicillin/clavulanate potassium may be associated with an increased risk of necrotizing enterocolitis in neonates.

Lactation: Ampicillin-class antibiotics are excreted in the milk; therefore, caution should be exercised when amoxicillin/Clavulanate potassium is administered to a nursing woman.

4.6 CONTRAINDICATIONS

Amoxicillin/clavulanate potassium is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with amoxicillin/clavulanate potassium.

4.7 SIDE EFFECTS

Amoxicillin/clavulanate potassium is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: Abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, muccocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

Hypersensitivity reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied be arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, hypersensitivity vasculitis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGOT) has been noted in patients treated with ampicillin-class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including hepatitis and cholestatic jaundice, increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphate, has been infrequently reported with amoxicillin/clavulanate potassium. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying

diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported.

Hernic and lymphatic systems: Anemia including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with amoxicillin/clavulanate potassium. There have been reports of increased.

Central Nervous system : Agitation, anxiety ,behavioral changes,confusion dizziness,insomnia and reversible hyper activity have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow or gray staining) has been rarely reported.Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

Prothrombine time in patients receiving amoxicillin/clavulanate potassium and anticoagulant therapy concomitantly.

5.1 INCOMPATIBILITIES

None

5.2 SHELF LIFE

36 Months

5.3 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from moisture.

5.4 NATURE AND CONTENTS OF CONTAINER

Dioclav 625 mg is packed in Alu-Alu foil laminated with LDPE. These strips ar packed as 7 x 2's tablets in a carton.

6. MARKETING AUTHORISATION HOLDER

National Pharmaceutical Industries Co. (SAOG)
P.O Box 120
Postal Code 124
Rusayl, Sultanate of Oman