1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Attached

SUMMARY OF PRODUCT CHARACTERISTICS
(PRODUCT DATA SHEET)

1. NAME OF THE MEDICINAL PRODUCT:
NOMEXICLAV DT 312.5 TABLETS (Dispersible Amoxicillin 250 mg and Potassium Clavulanate 62.5 mg Tablets BP)

2. COMPOSITION:
Qualitative & Quantitative Composition

Each uncoated dispersible tablet contains:
Amoxicillin Trihydrate BP
equivalent to Amoxicillin 250 mg
Potassium Clavulanate BP
(As diluted Potassium Clavulanate BP)
equivalent to Clavulanic Acid 62.5 mg
Excipients q.s.
For excipients refer 6.1

3 PHARMACEUTICAL FORM:
Tablets for Oral use

4 CLINICAL PARTICULARS:

4.1 Therapeutic Indication
Treatment of otitis media, sinusitis, and infections caused by susceptible organisms involving the lower respiratory tract, skin and skin structure, and urinary tract; spectrum same as amoxicillin with additional coverage of beta-lactamase producing B. catarrhalis, H. influenzae, N. gonorrhoeae, and S. aureus (not MRSA). The expanded coverage of this combination makes it a useful alternative when amoxicillin resistance is present and patients cannot tolerate alternative treatments

4.2 Posology and Method of Administration
Usual recommended dose : 20 mg/5 mg to 60 mg/15 mg for each kilogram of body weight a day, given in three divided doses.
For adults and children 540 kg: **1** tablet three times a day
Children <40 kg.
For children from 7 to 12 years: Amoxicillin 250 mg / Potassium Clavulanate 62.5 mg 3 times a day.
Elderly
No dose adjustment is considered necessary.

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals.

Method of administration
NOMEXICLAV DT 312.5 TABLETS are for oral use.
Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimize absorption of amoxicillin/clavulanic acid. Before taking NOMEXICLAV DT 312.5 TABLETS, it should be stirred into at least V2 glass water so that it will disperse (recommended for childeren <40 kg).

4.3 Contraindications
Amoxicillin is contra-indicated in patients with hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.
It is also contraindicated in patients with a previous history of severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporin, carbapenem or monobactam). It is also contraindicated in patients with a previous history of jaundice/hepatic impairment associated with amoxicillin and potassium clavulanate.

4.4 Special Warning and precautions for use

<u>Warnings</u>
Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients. Low incidence of cross-allergy with cephalosporins exists.
- Diarrhea: Incidence of diarrhea is higher than with amoxicillin alone.
- Hepatic effects: Although rare, hepatic dysfunction is more common in elderly and/or males, and occurs more frequently with prolonged treatment, and may occur after therapy is complete.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Infectious mononucleosis: A high percentage of patients with infectious mononucleosis have developed rash during therapy; ampicillin-class antibiotics not recommended in these patients.

- Renal impairment: Use with caution in patients with renal impairment;dosage adjustment recommended.

Dosage form specific issues:

- Clavulanic acid content: Due to differing content of clavulanic acid, not all formulations are interchangeable.
- Phenylalanine: Some products contain phenylalanine.

General Precautions

While amoxicillin and potassium 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 and potassium clavulanate 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.

4.5 Effects on ability to drive and use machine

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

4.6 Undesirable Effects

Amoxicillin and 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, mucocutaneous 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 by 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 (SGPT) 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 phosphatase, has been infrequently reported with amoxicillin and potassium clavulanate. 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.

Hemic and Lymphatic System: 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 and potassium clavulanate. There have been reports of increased prothrombin time in patients receiving amoxicillin and potassium clavulanate and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity 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.

4.7 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. 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.

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.

4.8 Interaction with other medicinal products and other forms of interaction

Allopurinol: May enhance the potential for allergic or hypersensitivity reactions to Amoxicillin. Risk C: Monitor therapy

Fusidic Acid: May diminish the therapeutic effect of Penicillins. Risk D: Consider therapy Modification

Methotrexate: Penicillins may decrease the excretion of Methotrexate. Risk C: Monitor Therapy

Mycophenolate: Penicillins may decrease serum concentrations of the active metabolite(s) of Mycophenolate. This effect appears to be the result of impaired enterohepatic recirculation. Risk C: Monitor therapy

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. Risk D: Consider therapy modification

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty2la strain is affected. Risk D: Consider therapy modification

Uricosuric Agents: May decrease the excretion of Penicillins. Risk C: Monitor therapy

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Amoxicillin and Potassium clavulanate is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the 13-lactamase inhibitor, Potassium clavulanate (the potassium salt of clavulanic acid).

Clavulanic acid binds and inhibits beta-lactamases that inactivate amoxicillin resulting in amoxicillin having an expanded spectrum of activity. Amoxicillin inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

5.2 Pharmacokinetic Properties

Amoxicillin and Potassium clavulanate are well absorbed from the gastrointestinal tract after oral administration of amoxicillin and Potassium clavulanate. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin and potassium clavulanate can be given without regard to meals, absorption of potassium clavulanate when taken with food is greater relative to the fasted state. In 1 study, the relative bioavailability of clavulanate was reduced when amoxicillin and potassium clavulanate was dosed at 30 and 150 minutes after the start of a high-fat breakfast. The safety and efficacy of amoxicillin and potassium clavulanate have been established in clinical trials where amoxicillin and potassium clavulanate was taken without regard to meals.

Amoxicillin serum concentrations achieved with amoxicillin and potassium clavulanate are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of amoxicillin and potassium clavulanate is 1.3 hours and that of clavulanic acid is 1.0 hour.

Approximately 50 % to 70 % of the amoxicillin and approximately 25 % to 40 % of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250 mg or 500 mg tablet of amoxicillin and potassium clavulanate.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Neither component in amoxicillin and potassium clavulanate is highly protein-bound; clavulanic acid has been found to be approximately 25 % bound to human serum and amoxicillin approximately 18 % bound.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the

brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

5.3 Preclinical safety Data:

Long-term studies in animals have not been performed to evaluate carcinogenic potential. The mutagenic potential of Amoxicillin and Potassium clavulanate 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. Amoxicillin and Potassium clavulanate 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 a 2:1 ratio formulation of amoxicillin:clavulanate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sr. No.	Name of Ingredients
1.	Microcrystalline Cellulose BP
2.	Sodium Starch Glycolate BP
3.	Crospovidone USP
4.	Magnesium Stearate BP
5.	Colloidal Anhydrous Silica BP
6.	Purified Talc BP
7.	Flavour Dry Orange IH DC-109
8.	Aspartame BP
9.	Instacoat Solution IC-S-344 IH
10.	Isopropyl Alcohol BP
11.	Dichloromethane BP

6.2 Incompatibilities: None known.

6.3 Shelf Life: 24 months.

6.4 Special Precaution for storage: Store below 25 ° C. Protect from light and moisture.
KEEP MEDICINE OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container:
1 Alu-Alu blister pack of 10 tablets each in a carton along with pack insert.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local Regulatory requirements.

7 MARKETING AUTHORISATION HOLDER
Name NOMEDI PHARMACEUTICALS LTD
Address : 387, Agege Motar Road,
Mushin, P.O.Box 11623,
Ilkeja, Lagos-Nigeria.
Phone : +234-8027000578,
E-mail : cliffordnzimako@yahoo.com

8 MARKETING AUTHORISATION NUMBER
42/UA/SC/P-2006

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
Not Applicable.

10 DATE OF REVISION OF THE TEXT
Not Applicable.

11 NAME AND ADDRESS OF MANUFACTURER
• CORAL LABORATORIES LTD.
Plot No: 27/28, Pharmacity,
Selaqui, Dehradun, Uttarakhand., India
Phone : +91 — 0135-2698422
+91 — 0135-2698466
Fax : + 91-0135-2699121
E-mail : doon@corallab.com