# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

**Moxypen Forte 500 mg Capsules**
Each capsule contains:
Amoxicillin (as Trihydrate) 500 mg

**Moxypen Forte 250 mg Powder for Suspension**
Each teaspoonful (5 ml) of suspension contains:
Amoxicillin (as Trihydrate) 250 mg

## 2. THERAPEUTIC INDICATIONS

Infections caused by amoxicillin - susceptible organisms.
Prevention of bacteremia in patients at risk of developing bacterial endocarditis.

## 3. THERAPEUTIC CLASSIFICATION

Antibiotic

## 4. ACTION AND CLINICAL PHARMACOLOGY

Moxypen Forte (amoxicillin) exerts its bactericidal action by interfering with bacterial cell wall synthesis.

## 5. CONTRAINDICATIONS

Moxypen Forte is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

A history of a previous hypersensitivity reaction to any of the penicillins or cephalosporins is a contraindication.

Moxypen Forte (amoxicillin) is also contraindicated in cases where infectious mononucleosis is either suspected or confirmed.

## 6. WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients following oral dosing of penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with cephalosporins. Before initiating therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other allergens. If an allergic reaction occurs, administration of Moxypen Forte (amoxicillin) should be discontinued and appropriate therapy instituted.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Hypersensitivity reactions are more likely to occur in patients with a history of hypersensitivity to beta-lactams.

Abnormal prolongation of prothrombin time (increased international normalized ratio (INR)) has been reported in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when amoxicillin and oral anticoagulants are prescribed concurrently, particularly upon initiation or cessation of concurrent administration. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

**Severe Cutaneous Adverse Reactions**

Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment. When SCAR is suspected, MOXYPEN FORTE should be discontinued and appropriate therapy and/or measures should be taken.

**Gastrointestinal**

**Clostridium difficile-associated disease**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including amoxicillin (see sec. 8- **ADVERSE REACTIONS**). CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against Clostridium difficile. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against Clostridium difficile. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

**Susceptibility/Resistance**

**Development of Drug Resistant Bacteria**

Prescribing Moxypen Forte in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

## 7. PRECAUTIONS

Periodic assessment of renal, hepatic and hematopoietic functions should be made during prolonged therapy with Moxypen Forte (amoxicillin).

Because amoxicillin is excreted mostly by the kidney, the dosage for patients with renal impairment should

be reduced in proportion to the degree of loss of renal function.

Use in the Elderly: There are no known specific precautions for the use of amoxicillin in the elderly.

If superinfections with mycotic or bacterial pathogens occur (usually involving Aerobacter, Pseudomonas or Candida) treatment with Moxypen Forte should be discontinued and appropriate therapy instituted.

The safety of Moxypen Forte in the treatment of infections during pregnancy has not been established. If the administration of Moxypen Forte to pregnant patients is considered to be necessary, its use requires that the potential benefits be weighed against the possible hazards to the fetus.

A morbilliform rash following the use of ampicillin in patients with infectious mononucleosis has been well documented and has also been reported to occur following the use of amoxicillin.

**Important information about some of the excipients- Moxypen Forte 250 Suspension:**

Moxypen Forte 250 Suspension contains about 3 g sucrose per 5 ml. Therefore, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Moxypen Forte 250 mg Powder for Suspension contains 2.79 mg sodium benzoate (E211) in each 5 ml. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

Moxypen Forte 250 mg Powder for Suspension contains about 1.5mg benzyl alcohol, which may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children. Do not give to newborn baby (up to 4 weeks old), unless recommended by the doctor. Do not use for more than a week in young children (less than 3 years old), unless advised by the doctor. Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”). Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).

Moxypen Forte 250 Suspension contains FD&C red #40 (E129) which may cause allergic reactions.

Moxypen Forte 250 mg Powder for Suspension contains 3.20 mg per 5 ml, less than 1 mmol sodium (23 mg) per 5 ml, that is to say essentially "sodium-free".

## 8. ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be related to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and cephalosporins and in those with a history of allergy, asthma, hay fever or urticaria.

The following adverse reactions have been reported as associated with the use of Moxypen Forte:

**Gastrointestinal -** Nausea, vomiting and diarrhea, hemorrhagic and pseudomembranous colitis. Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including amoxicillin. Glossitis, black "hairy" tongue and stomatitis, mucocutaneous candidiasis, tooth discoloration (brown, yellow or gray staining); most reports occurred in pediatric patients. Discoloration

was reduced or eliminated with brushing or dental cleaning in most cases.

**Hypersensitivity Reactions** - Skin rashes have been reported frequently. Less commonly, a few cases of serum sickness like reactions including urticaria, erythema, erythema multiforme, angioneurotic edema, pruritus have been reported. Rarely, Stevens- Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, exfoliative dermatitis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis have been reported.

**Anaphylaxis** is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

NOTE: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and if necessary, systemic corticosteroids. Whenever such reactions occur, Moxypen Forte (amoxicillin) should be discontinued unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to amoxicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen and intravenous steroids.

**Hepatobiliary** - A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is not known. Transient increases in serum alkaline phosphatase and lactic dehydrogenase levels have also been observed but they returned to normal on discontinuation of amoxicillin. Reports have also been seen of hepatic dysfunction including cholestatic jaundice, hepatic cholestasis, acute cytolytic hepatitis,

**Hemic and Lymphatic Systems** - Anemia thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, neutropenia and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be a hypersensitivity phenomena. Reports have also been seen of anemia including hemolytic anemia.

**Central Nervous System** - As with other penicillins, acute and chronic toxicity is not a clinical problem. Although penicillins do not normally cross the blood-brain barrier to any substantial extent, if massive doses are given (several grams per day) to elderly patients, patients with inflamed meninges or patients with impaired renal function, toxic reactions are likely to occur. At extremely high doses, convulsions can occur. When penicillin reaches a high concentration in the cerebrospinal fluid, neurotoxic symptoms consisting of myoclonia, convulsive seizures and depressed consciousness may occur. Unless administration of the drug is stopped or its dosage reduced, the syndrome may progress to coma and death. Dizziness, hyperkinesias, hyperactivity, agitation, anxiety, insomnia, confusion, and behavioural changes have also been reported.

**Skin and Appendages** - erythematous maculopapular rash.

**Renal** - Crystalluria. Interstitial nephritis (oliguria, proteinuria, hematuria, hyaline casts, pyuria) and nephropathy are infrequent and usually associated with high doses of parenteral penicillins; however, this has occurred with all of the penicillins. Such reactions are hypersensitivity responses and are usually associated with fever, skin rash and eosinophilia. Elevations of creatinine or blood urea nitrogen may occur.

**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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

## 9. DRUG INTERACTIONS

**Methotrexate:** Penicillins compete with renal tubular secretion of methotrexate, resulting in decreased clearance of methotrexate. Concomitant use may increase methotrexate serum concentrations, with increased risk of toxicity.

**Probenecid:** Probenecid inhibits the renal tubular excretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.

**Warfarin:** Abnormal prolongation of prothrombin time (increased international normalized ratio [INR]) has been reported in patients receiving amoxicillin and warfarin. Appropriate monitoring should be undertaken when warfarin is prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

**Oral Contraceptives:** Moxypen Forte may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

**Tetracyclines:** Bacteriostatic action of tetracyclines may inhibit bactericidal activity of penicillins.

## 10. SYMPTOMS AND TREATMENT OF OVERDOSAGE

Treatment of overdosage would likely be needed only in patients with severely impaired renal function, since patients with normal kidneys excrete penicillins at a fast rate. Hemodialysis would, therefore, represent the main form of treatment.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

## 11. DOSAGE AND ADMINISTRATION

With the exception of gonorrhea, treatment with Moxypen should be continued for a minimum of 48-72 hours beyond the time at which the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.
In the treatment of group A β-hemolytic streptococcal infections, therapy with this drug should be continued for at least 10 days to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

Upper Respiratory Tract and Chest Infections
*Adults and Children over 10 Years of Age:*
The recommended dosage is 250-500 mg 3 times daily, every 8 hours.

*Infants and Children under 10 Years of Age:*
In infants under 2 years of age, the dosage is 62.5 mg 3 times daily, every 8 hours.
In children 2-10 years of age, the dosage is 125 mg 3 times daily, every 8 hours. For more severe infections, the dosage may be increased to 250 mg 3 times daily.

The recommended dosage according to body weight is 20 mg/kg per day in divided doses every 8 hours. For more severe infections, the dosage may be increased to 40 mg/kg body weight per day every 8 hours.

Skin and Soft-tissue Infections
Treat as for upper respiratory tract and chest infections.

Uncomplicated Lower Urinary Tract Infections
*Adults*
A single dose of 3 g may be administered.
*Children*
A single dose of 100 mg/kg body weight may be administered.

Gonorrhea
A single dose of 3 g may be administered.

Prophylaxis of Bacterial Endocarditis (in dental procedures)
*Adults and Children over 10 Years of Age*
A single dose of 3 g about 1 hour prior to the procedure, to prevent bacteremia.

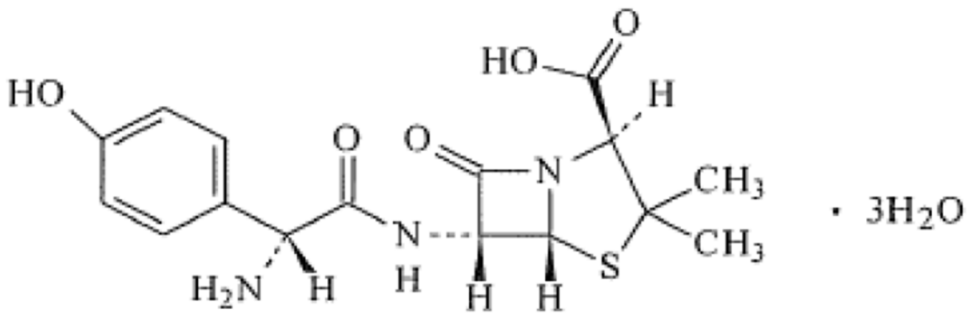
*Children under 10 Years of Age*
Half the adult dose.

In order to obtain optimal absorption of drug from Moxypen Forte capsules they should be administered between meals with a glass of water (250 mL or 8 fl. oz.).

## 12. PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Trade Name: MOXYPEN FORTE
Proper Name: Amoxicillin Trihydrate
Chemical Name: Trihydrate of 6-[D-(-)-alpha-amino-4-hydroxyphenyl-acetamido] penicillanic acid.
Structural Formula:




Molecular Formula: $C_{16}H_{19}N_3O_5S*3H_2O$

Molecular Weight: 419.5

Description: Amoxicillin trihydrate is a white practically odourless crystalline powder, slightly soluble in water and in methanol; insoluble in benzenes, in chloroform and in ether.

LIST OF EXCIPIENTS

**Moxypen Forte 500 mg Capsules**
Magnesium stearate

Capsule shell: gelatin, FD&C red #3 (erythrosine E127), titanium dioxide, FD&C blue # 2 (E132).
Printing ink: titanium dioxide, dehydrated alcohol, isopropyl alcohol, shellac, povidone, butyl alcohol, propylene glycol, sodium hydroxide.

**Moxypen Forte 250 mg Powder for Suspension**
Sucrose, spray dried artificial flavor (cherry raspberry type), silicon dioxide, sodium citrate anhydrous, xanthan gum, sodium benzoate, FD&C red # 40.

STABILITY AND STORAGE RECOMMENDATIONS:

Shelf life of unopened packages:
The expiry date of the product is indicated on the packaging materials.

**Moxypen Forte 500 mg Capsules**
Store in a dry place below 25°C.
Shelf life after opening (bottle presentation): to be used within 1 month after first opening the bottle.

**Moxypen Forte 250 mg Powder for Suspension**
Store the powder in a dry place, below 25°C.
Shelf life after reconstitution:
The prepared suspension should be kept in the refrigerator (2º-8ºC) or at room temperature (25ºC) and should be used within 14 days.

DIRECTIONS FOR DISPENSING Moxypen Forte 250 mg Powder for Suspension:

Add 36 ml or 60 ml of distilled water to prepare 60 ml or 100 ml of suspension accordingly: tap bottle to loosen powder, add the water and shake well.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 13. AVAILABILITY OF DOSAGE FORMS

**Moxypen Forte 500 mg Capsules**

Opaque maroon cap and opaque maroon body, hard gelatin capsules. Printed white MOXYPEN over 500 on the cap and FORTE over teva logo on body portion of the capsules.

There are two package types:
Blisters: 10 or 20 capsules.
Bottle: 20 capsules.
Not all pack sizes may be marketed.

**Moxypen Forte 250 mg Powder for Suspension**
Finely granulated, off white to pinkish powder.

After adding water, a pink-colored liquid will be obtained.

There are two package sizes:
A package containing powder for preparation of 60 ml of suspension,
A package containing powder for preparation of 100 ml of suspension

## 14. MICROBIOLOGY

In vitro studies with amoxicillin have demonstrated the susceptibility of the following gram-positive bacteria: beta-hemolytic streptococci, Streptococcus pneumoniae, D. pneumoniae, non-penicillinase-producing staphylococci, and Streptococcus faecalis. It is active in vitro against many strains of Haemophilus influenzae, Neisseria gonorrhoeae and Proteus mirabilis. Because amoxicillin does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci.

Amoxicillin is not active against all Pseudomonas aeruginosa, indole-positive Proteus species, Serratia marcescens, Klebsiella, and Enterobacter species.

Disc Susceptibility Tests: Quantitative methods that involve the measurement of the diameters of zones of inhibition can be used to estimate micro-organism sensitivity to a particular antibiotic. A procedure which involves the use of discs impregnated with a particular antibiotic has been described for the ampicillin class of antibiotics. Interpretations correlate diameters of the zones of inhibition with MIC values for amoxicillin. With this procedure, using a 10 pg disc, a zone of 29 mm or more is classified as "susceptible" and indicates that the infecting organism is likely to respond to therapy. A zone of 20 mm or less is classified as "resistant" and indicates that the infecting organism is not likely to respond to therapy. A zone of 21 -28 mm is classified as "intermediate susceptibility" and indicates that the organism would be susceptible if high dosages are used, or if the infection is confined to tissues and fluids (e.g., urine), in which antibiotic levels are attained.

The in vitro activity of amoxicillin against selected organisms has been reported by Sutherland et al. and Sabto et al. shown in the following tables:

Table I. *In Vitro* Activity of Amoxicillin Against Gram-Positive Cocci, H. Influenzae and N. Gonorrhoeae

| Organism | No. of Strains | Minimum Inhibitory Concentration (µg/mL) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | .005 | 0.01 | 0.02 | 0.03 | 0.05 | 0,12 | 0.25 | 0.5 | 1.0 |
| Staphylococcus aureus | 29 | | | | | 3 | 20 | 6 | | |
| Bela-hemolytic streptococci | 28 | | 25 | 3 | | | | | | |
| Streptococcus pneumoniae | 23 | | 9 | 6 | 2 | 6 | | | | |
| Streptococcus faecalis | 53 | | | | | | | 3 | 39 | 11 |
| H. influenzae | 98 | | | | | | 20 | 41 | 29 | 8 |
| N. gonorrhoeae | 13 | | 1 | 3 | | 3 | 1 | 5 | | |

Table II. *In Vitro* Activity of Amoxicillin Against Gram-Negative Bacilli

| Organism | No, of Strains | Minimum Inhibitory Concentration (µg/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1.25 or less | 2.6 | 5.0 | 12.5 | 25 | 50 | 100 | >100 |
| Proteus mirabilis | 90 | 38 | 28 | 11 | | | | | 13 |
| Shigella sonnei | 26 | | 4 | 11 | 4 | | 1 | 1 | 5 |
| Salmonella species | 20 | 10 | 8 | | | | | | 2 |
| Klebsiella-Enterobacter | 29 | | 1 | | | | 1 | 2 | 25 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Serratia marcescens | 18 | | | 1 | | 1 | 3 | 6 | 7 |
| E. coli | 206 | 5 | 13 | 115 | 46 | 2 | 1 | 1 | 23 |

The minimum inhibitory concentrations of amoxicillin against all micro-organisms with the exception of 5 strains of Streptococcus pneumoniae were measured by serial dilution in agar. The minimum inhibitory concentration against these strains of Streptococcus pneumoniae was estimated using the tube dilution method with Levinthal's medium.[34]

## 15. PHARMACOLOGY

Amoxicillin is stable in the presence of gastric acid. Moxypen Forte is rapidly and well absorbed after oral administration to fasting subjects. It was found in a recent study that peak serum antibiotic levels were reduced by 50% in subjects receiving amoxicillin immediately following a standard meal. Reducing the dose-water volume given with amoxicillin from 250 to 25 mL in fasted subjects also caused a significant reduction in serum amoxicillin levels. This may be due to the low water solubility of amoxicillin trihydrate (1 g in 370 mL water). In addition, food ingestion immediately before dosing also reduced the urinary excretion.

Peak serum levels are attained between 1 and 2 hours after drug administration. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid. Amoxicillin is excreted largely unchanged in the urine while 10-25% of the administered dose is excreted in the form of penicilloic acid. The excretion of amoxicillin can be delayed by concurrent administration of probenecid. Amoxicillin is not highly protein bound. In blood serum, amoxicillin is approximately 17-1 8% protein bound compared to 59% for penicillin G.

The following amoxicillin mean serum levels were found following the administration of 250 mg capsules of Moxypen Forte to 12 healthy adult volunteers:

| Time (hr.) | 0.5 | 1.0 | 1.5 | 2 | 3 | 4 | 5 | 7 |
|---|---|---|---|---|---|---|---|---|
| Mean Serum Levels (µg/mL) | 0.81 | 2.96 | 3.17 | 3.10 | 2.22 | 1.12 | 0.50 | 0.11 |

Peak blood serum levels averaged 3.8 µg/mL (range 2.35 to 6.38) and the $T_{max}$ was 1.50 hr. The mean biological half-life ($t_{1/2}$) was found to be 55.8 minutes with a mean elimination rate constant $K_{el}$ of 0.7456 $hr.^{-1}$.

Twelve normal male subjects participated in a bioavailability study of Moxypen Forte Granules for Suspension. Each subject was given 5 mL (250 mg) of reconstituted Moxypen Forte Granules for Suspension in a single dose.

The following amoxicillin mean serum levels were found:

| Time (hr.) | 0.5 | 1.0 | 1.5 | 2 | 3 | 4 | 5 | 7 |
|---|---|---|---|---|---|---|---|---|
| Mean Serum Levels (µg/mL) | 3.26 | 4.19 | 3.40 | 2.56 | 1.65 | 0.98 | 0.43 | 0.10 |

Peak plasma concentrations from 2.65 to 5.75µg/mL were obtained with a mean $C_{max}$ of 4.24 + 0.74 µg/mL. The

time required to reach peak concentrations ranged from 0.5 to 1.5 hours, with a $T_{max}$ mean of 1 .00 + 0.21 hr.

The AUC's calculated for 0 to 7 hours ranged from 8.475 to 12.865µg-hours/mL. The mean AUC was 10.713 + 1.443 µg-hours/mL. The mean biological half-life for Moxypen Forte Granules far Suspension was 26.4 minutes. The mean elimination rate constant ($K_{el}$) was 1.57 $hour^{-1}$.

The administration of 500 mg amoxicillin to healthy fasting subjects has been reported to produce peak mean serum levels of 10.8µg/mL and 6.75µg/mL. Additional studies in healthy volunteers with normal renal function receiving 500 mg doses, indicated that peak serum levels could vary from 5.0 to 10.8µg/mL. Serum amoxicillin half-life values reported in the literature vary from 1-1.3 hours. About 60-80% of an oral dose of amoxicillin is excreted in the urine. In the presence of renal impairment the serum half-life increases (between 7 and 10 hours), necessitating a reduction in the dosage administered.

## 16. TOXICOLOGY

Acute Toxicity

The fallowing $LD_{50}$ values for amoxicillin expressed in mg/kg of body weight have been reported.

| Species | Route of Administration | | |
|---|---|---|---|
| | P.O. | I.P. | S.C. |
| Mouse | > 10,000 | 4350 | > 6,000 |
| Rat | > 8.000 | 4900 | > 6,000 |
| Dag | > 3,000 | - | - |

Sub-acute Toxicity

Rats:
In one study male and female rats were orally administered 500 mg/kg amoxicillin daily for 21 days. With the exception of significantly greater ($p<0.01$) BUN values in the female test group compared with controls, there were no toxic effects on the organs, tissues or fluids of the body, nor any adverse effects on food consumption, weight gain, or efficiency of food utilization reported in the study.

Histopathologic evaluation of tissues revealed a minimal degree of fatty change in livers of treated females. However, this finding was not considered a toxic change but related to a possible alteration in the intestinal flora.

Dogs:
One male and one female dog were dosed orally with 250 mg/kg amoxicillin daily for 14 days. During the period of observation, no deaths occurred, no adverse changes in body weight and no effect on food consumption was found. Laboratory values were found within normal limits. At post-mortem, no gross or microscopic abnormalities were reported and organ weights were within normal limits.

Chronic Toxicity

Rats:
In one study male and female rats were given oral doses of 200, 500 and 2000 mg/kg/day amoxicillin, 6 days a week for 26 weeks. No apparent disturbances in absolute organ weights of either treated male or

female animals were noted nor was any histologic evidence of response to treatment observed.

In another study, 3 groups of Sprague-Dawley rats were given oral doses of 200, 500 and 2000 mg/kg of amoxicillin for a test period of 13-15 weeks. There were no gross or histologic changes observed in the treated rats that were considered related to the administration of amoxicillin. Some of the intermediate and low-dose groups were shown to exhibit body weight gains lower (males) or slightly higher (females) than those of the control animals.

Dogs:
It has been reported that amoxicillin was administered orally at doses of 200, 500 and 2000 mg/kg/day to male and female dogs for a period of 6 months. (Groups consisted of 6 male and 6 female dogs initially, but after 3 months dosing, each group was reduced to 3 dogs).

During the first six weeks of treatment, occasional bouts of vomiting, one to four hours after dosing, were reported in dogs receiving 2000 mg/kg/day and 4 bouts of vomiting were recorded in dogs receiving the intermediate dose of 500 mg/kg/day. Grey coloured feces were seen on very isolated occasions in dogs treated at high and intermediate dose levels only. On seven occasions it involved dogs receiving the highest dose level (2000 mg/kg/day) and on three occasions dogs receiving the intermediate dose level (500 mg/kg/day).

Body weight gains of treated males were reported to be not significantly different from those of controls, but all dosed females increased in weight at a significantly slower rate than did the controls. This factor was reported to be attributable to excessive weight gain in the control animals. Food and water consumption was not affected. No abnormalities of the eyes were observed attributable to amoxicillin.

In a second study 2 groups of Beagle dogs were given oral doses of 500 mg/kg and 200 mg/kg of amoxicillin for 13 weeks. There were no gross or histologic changes reported in the treated dogs that were considered related to the administration of amoxicillin.

Effects on Fertility and Reproductive Performance

Rats:
Daily doses of 200 and 500 mg/kg amoxicillin were administered orally in one reported study. Male rats that had attained a minimum age of 40 days were treated for 63 days and sexually mature females for 14 days prior to mating. Dosing continued throughout the remainder of the investigation. The duration of gestation was unaffected by treatment at either dosage. It was noted that pregnancy rate at 500 mg/kg was slightly lower than that of controls at the first and second mating. At 200 mg/kg, the pregnancy rate was essentially comparable to control values at both mating. The chronologic sequence of mating was comparable for all groups; at 500 mg/kg, the total number of animals showing evidence of mating was slightly lower than that of controls at both pairings. Pre- and post-implantation losses were comparable for all groups at the first and second pregnancies.

Among the rats allowed to rear their young, litter sizes, litter weights, mean pup weights and the pup mortality rates for the group dosed at 500 mg/kg amoxicillin were comparable to control values at birth, 4 and 21 days postpartum. Mean pup weights and pup mortality rates were similarly unaffected by 200 mg/kg amoxicillin; but litter sizes and litter weights were lower than control values from birth through lactation. These differences were considered to be unrelated to treatment. No abnormal young were observed.

Effects on Pregnancy

Mice:
It has been reported that amoxicillin administered at doses of 200, 500 and 2000 mg/kg/day orally during

days 6-1 5 of pregnancy produced no obvious signs of reaction to treatment or deaths among parent animals. Body weight changes of pregnant dams were comparable for all groups, as was the pregnancy rate.

Fetal loss was significantly higher among all test groups than among controls. However, as implantation rates also tended to be higher at the 500 and 2000 mg/kg doses, litter sizes were only marginally, and not significantly, lower than the control value. Litter sizes and implantation rate also tended to lie at or above the upper limit of the laboratory range. Due to the latter factors, the biologic importance of the increased fetal loss was uncertain. It was noted that mean pup weights were comparable for all groups. The distribution of skeletal variants was considered to be unaffected by treatment at any dosage. A significantly higher proportion of pups with cervical ribs was found in the 200 mg/kg dose group. Cervical rib and 14th rib are the prolongations of the transverse processes of the cervical or lumbar vertebrae. Supernumerary ribs have an incidence which depends on the strain of animals. Cervical ribs are not abnormalities and have no pathologic significance.

In this experiment the incidence of cervical ribs was 12% in control rats and 16% in the drug-treated groups if the three groups are calculated together. If the groups are considered individually, then in the lowest dose group (200 mg/kg) the incidence of cervical ribs was 24%, which is, statistically, significantly higher than in the controls. This finding was not considered to be drug related since at the 500 mg/kg dose level the incidence of cervical ribs was significantly lower than in controls. At the highest dose level (2000 mg/kg) the incidence of cervical ribs was 17%, similar to the controls. The incidence of visceral abnormalities was not significantly affected at any dose level.

Rats:
Amoxicillin was administered at doses of 200 mg/kg, 500 mg/kg and 1000 mg/kg orally during gestation from day 6 through 15. Amoxicillin did not modify pregnancy, percentage of resorption and did not produce fetal abnormalities as compared with negative control rats.

Effects on Peri- and Post-Natal Development of the Rat

Amoxicillin was administered orally at 200 and 500 mg/kg/day from day 15 of gestation through lactation to 21 days post-partum. Body weight gain, pregnancy rate, and the duration of gestation of parent animals were unaffected by treatment at any dosage. There was a significant dose-related trend to lower litter size and weight at birth. This persisted through lactation to weaning despite reduced pup mortality and increased mean pup weight in the test groups compared with controls. No abnormal young were observed.

## 17. LICENCE HOLDER AND MANUFACTURER

**Licence holder:**
Teva Israel Ltd.
124 Dvora Hanevi'a St. Tel Aviv 6944020

**Manufacturer:**
Teva Canada Limited,
Toronto, Ontario, Canada.

## 18. REGISTRATION NUMBERS

Moxypen Forte 500 mg Capsules: 130.22.30823.
Moxypen Forte 250 mg Powder for Suspension: 132.01.31050

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