Cefobid

Cefoperazone sodium

0.5, 1 and 2 g Powder for solution for injection or infusion.

Reference Market : Austria

Egypt

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CEFOBID 0.5 g – 1.0 g - 2.0 g Dry-fill vials

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefobid 0.5 gm : Vial contains Cefoperazone sodium 0.538 g equivalent to Cefoperazone anhydrous 0.5 g.

Cefobid 1 gm: Vial contains Cefoperazone sodium 1.055 g equivalent to Cefoperazone anhydrous 1 g.

Cefobid 2 gm: Vial contains Cefoperazone sodium 2.099 g equivalent to Cefoperazone anhydrous 2 g.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
White to off-white powder free from visible contamination, yielding a clear solution essentially free from foreign matter and un- dissolved solid after reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dry-fill vials are indicated for

treatment of the following systemic and/or local infections caused by cefoperazone-susceptible microorganisms:

- Upper and lower respiratory tract infections, e.g. pneumonia, acute and chronic bronchitis
- Upper and lower urinary tract infections, e.g. pyelonephritis, urethritis
- Peritonitis, cholecystitis, cholangitis and and other intraabdominal infections
- Septicemia
- Skin and soft tissue infections, e.g. cellulitis
- Bone and joint infections, e.g. osteomyelitis
- Pelvic infections, such as endometritis and other infections of the genital tract including gonorrhea, in combination with other broad-spectrum antibiotics, if necessary

and prophylaxis of postoperative infections in connection with abdominal surgery, gynecological, cardiac and vascular surgery as well as orthopedic surgery.

National and international recommendations for proper use of antimicrobial substances have to be considered when using Cefobid 2 g – dry-fill vials.

4.2 Posology and method of administration

Administration

Intermittent i.v. infusion, i.v. injection, i.m.injection

Instructions for administration

Intermittent intravenous infusion

Each 1 g or 2 g Vial of Cefobid are dissolved in 20-100 ml of a compatible, sterile injection solution (i.e. sterile water for injection; 5% dextrose with or without lactated Ringer's solution, or with 0.9% or 0.2% sodium chloride; 10% dextrose solution; lactated Ringer's solution; 0.9% sodium chloride) and then infused over a period of 15 minutes to one hour (because the solution is hypotonic, an amount of 20 ml of sterile water for injection should not be exceeded).

Intravenous Administration

Vials of CEFOBID sterile powder may be initially reconstituted with a minimum of 2.8 ml per gram of cefoperazone of Sterile water for injection. For ease of reconstitution the use of 5 ml sterile water for injection per gram of CEFOBID is recommended.

For direct intravenous injection, the maximum dose of CEFOBID should be two grams per administration for adults and 50 mg/kg per administration for children. The drug should be dissolved in sterile water for injectionto give a final concentration of 100 mg/ml and administered over a period of no less than three minutes to five minutes.

Intramuscular Administration

Sterile Water for injection or Bacteriostatic Water for injection may be used to prepare CEFOBID for intramuscular injection. When concentrations of 250 mg/ml or more are to be administered, a lidocaine solution should be used. These solutions should be prepared using a combination of Sterile Water for Injection and 2% Lidocaine Hydrochloride Injection that approximates a 0.5% Lidocaine Hydrochloride Solution. A two-step dilution process as follows is recommended. First, add the required amount of Sterile Water for injection and agitate until CEFOBID powder is completely dissolved. Second, add the required amount of 2% lidocaine and mix.

	Final Cetoperazone concentration	**Step 1 Volume of sterile water**	**Step2 Volume of 2%Lidocaine**	**Withdrawable Volume***
0.5 g vial	250mg/ml 333mg/ml	1.3 ml 0.9 ml	0.4 ml 0.3ml	2.0ml 1.5ml
1.0 g vial	250mg/ml 333mg/ml	2.6ml 1.8 ml	0.9ml 0.6ml	4.0ml 3.0ml
2.0 g vial	250mg/ml 333mg/ml	5.2ml 3.7ml	1.8ml 1.2ml	8.0ml 6.0ml

**There* is *sufficient excess present to allow* for *withdrawl* and *administration of the stated volumes*.

The drug should be given by deep intramuscular injection into the large muscle mass of the gluteus maximum or anterior thigh.

Dosage

Adults

The usual adult daily dose is 2 - 4 g, divided in two equal doses every 12 hours; in severe infections, the dose may be increased to 8 g daily in divided doses. Even daily doses of up to 16 g (2 x 8 g) have been tolerated without complications.

The recommended dosage for uncomplicated gonococcal urethritis is 500 mg i.m. as a single dose.

For perioperative prophylaxis, 1 - 2 g Cefobid should be administered intravenously approximately 0.5 - 1.5 hrs prior to the start of surgery. The dose may be repeated every 12 hours. Prophylactic administration should be restricted to a maximum of 72 hours.

Infants and children (1 month – 11 years)

The recommended dosage in infants and children is 50 - 200 mg/kg body weight/ day in divided doses every 8 to 12 hours. The maximum dose should not exceed 12 grams/day.

Use in renal dysfunction

Daily doses of 2 x 1 g or 2 x 2 g Cefobid may be administered irrespective of the degree of renal dysfunction. For patients whose glomerular filtration rate is less than 18 ml/min or whose serum creatinine level is greater than 3.5 mg/ dl, the maximum dosage is 4 g per day.
Serum half-life of Cefoperazone is slightly reduced during hemodialysis. Dosage should be adjusted according to dialysis requirements.

Use in patients with hepatic dysfunction or coexisting renal and hepatic dysfunction

In patients with hepatic dysfunction and/or biliary obstruction, serum half-life is usually prolonged and renal excretion of cefoperazone is increased.
Dosage adjustment may be necessary in cases of severe biliary obstruction, severe hepatic dysfunction or coexisting renal dysfunction.
In patients with both severe renal and hepatic disease, plasma concentrations of cefoperazone should be monitored regularly and dosage adjusted as necessary. In these patients, the dosage should not exceed 2 g daily without close monitoring of serum concentrations. (See also section 4.4 Special warnings and precautions for use)

Elderly patients

There are no special data available on pharmacokinetic parameters in elderly patients.

Duration of treatment

The duration of treatment depends on the course of the disease. Cefobid therapy should be continued for at least 3 days after the patient's temperature has returned to normal.

Combination therapy

In patients with severe, life-threatening infections, combination therapy with Cefobid and an aminoglycoside may be indicated. Because of physical incompatibility, the two drugs must not be mixed nor injected at the same time or at the same site. The solutions should be prepared shortly before injection. (See also sections 4.5 Interactions with other medicinal products and other forms of interaction and 6.2 Incompatibilities)
In case of a combination therapy with aminoglycosides, renal function must be carefully monitored (see also section 4.4 Special warnings and precautions for use). In these cases also the contraindications of the aminoglycoside have to be considered.

4.3 Contraindications

Hypersensitivity to the active substance and/or other cephalosporins.
In penicillin-sensitive patients, a possible cross allergy (5 - 10%) needs to be considered.

Cefoperazone is contraindicated in patients in whom administration of vitamin K is contraindicated (especially patients with tendency to hemorrhages).

4.4 Special warnings and precautions for use

Hypersensitivity
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam or cephalosporin therapy including cefoperazone. These reactions are more apt to occur in individuals with a history of hypersensitivity reactions to multiple allergens.

Before therapy with cefoperazone is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. This product should be given cautiously to penicillin sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs.

If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe and occasionally fatal skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and dermatitis exfoliative have been reported in patients on cefoperazone therapy. If a severe skin reaction occurs cefoperazone should be discontinued and appropriate therapy should be initiated (see section 4.8 Undesirable effects).

Use in Hepatic Dysfunction
Cefoperazone is extensively excreted in bile. The serum half-life of cefoperazone is usually prolonged and urinary excretion of the drug increased in patients with hepatic diseases and/or biliary obstruction. Even with severe hepatic dysfunction, therapeutic concentrations of cefoperazone are obtained in bile and only a 2 to 4 fold increase in half life seen (see section 4.2 Posology and method of administration).

General
Serious hemorrhage cases, including fatalities, have been reported with cefoperazone. Those at risk include patients with poor diet, malabsorption states and patients on prolonged intravenous alimentation regimens.-These patients should be monitored for signs of bleeding, thrombocytopenia, and hypoprothrombinemia. Cefoperazone should be discontinued if there is persistent bleeding and no alternative explanations are identified.
Additional factors increasing the risk of hemorrhages and resulting conditions include malignancies, hepatic and/or renal dysfunction, old age, thrombocytopenia, concomitant diseases inducing or increasing hemorrhagic tendencies (e.g. hemophilia, gastrointestinal ulcers), long-term antibiotic treatment. Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated.

As with other antibiotics, overgrowth of nonsusceptible organisms may occur during prolonged use of cefoperazone. Patients should be observed carefully during treatment. If resistance or selection of organisms occur, a different antibiotic should be used.

As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during extended therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important when treating infants.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefoperazone, 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.

In case of severe and persisting diarrhea cefoperazone therapy should be discontinued immediately and appropriate treatment initiated (e.g. oral vancomycin, 4 x 250 mg). Peristalsis-inhibiting drugs are contraindicated.

Cefoperazone should be administered with caution in patients with a history of enterocolitis.

During and up to 5 days after cefoperazone therapy, **alcohol consumption and administration of drugs containing alcohol** must be avoided (see also section 4.5 Interactions with other medicinal products and other forms of interaction).

Although there is no evidence that cefoperazone alone has a nephrotoxic potential, renal function should be monitored if the drug is administered in conjunction with aminoglycosides (see also section 4.2 Posology and method of administration).

Usage in Infancy
Cefoperazone has been effectively used in infants. It has not been extensively studied in premature infants and neonates.

In neonates with kernicterus, cefoperazone does not displace bilirubin from plasma protein binding sites.

Cefobid 0.5 gm contains 17 mg sodium per vial, Cefobid 1 gm contains 34 mg sodium per vial, Cefobid 2 gm contains 68 mg sodium per vial. This has to be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interactions

Antabuslike reactions (flushing, sweating, headache and tachycardia) have been observed when alcohol was ingested during and as late as the fifth day after administration of cefoperazone. A similar reaction has also been reported with other cephalosporins. Therefore, alcohol consumption should be avoided during and up to 5 days after cefoperazone therapy. For patients requiring oral or parenteral artificial feeding, solutions containing ethanol should be avoided. (See also section 4.4 Special warnings and precautions for use)

If high doses of **heparin and oral anticoagulants** are administered in conjunction with cefoperazone, coagulation parameters should be monitored frequently and regularly. This also applies to concomitant administration of substances affecting thrombocyte function.

Since nephrotoxic reactions have occurred with concomitant administration of **aminoglycosides** and cephalosporins, renal function should be monitored in such cases. In case of a combination therapy with an aminoglycoside antibiotic, the two drugs must not be injected together because of physical incompatibility (see also sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use and 6.2 Incompatibilities).

Although no impairment of renal function has been observed with concomitant administration of Cefobid and **furosemide**, it should be borne in mind that renal function may be impaired due to co-administration of cephalosporins and strongly acting saluretics.

Drug Laboratory Test Interactions
A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution.

4.6 Fertility, pregnancy and lactation

Pregnancy
Reproduction studies have been performed in mice, rats and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility and did not show any teratological findings. However, since there are no adequate and well-controlled studies in pregnant women and animal

reproduction studies are not always predictive of human response, this drug should be used during pregnancy only in life-threatening situations.

Lactation
Since small quantities of cefoperazone are excreted in human milk, cefoperazone should not be used during lactation period.

4.7 Effects on ability to drive and use machines

Cefobid has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

For the classification of frequencies of side effects, the following categories are used:
Very Common: ≥ 1/10
Common: ≥ 1/100 and < 1/10
Uncommon: ≥ 1/1000 and < 1/100
Rare: ≥ 1/10,000 and < 1/1000
Very Rare: < 1/10,000
Not known (cannot be estimated from the available data)

System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Not known**
Blood and lymphatic system disorders	Haemoglobin decreased Haematocrit decreased Eosinophilia	Neutropenia[1] Neutrophil count decreased Coombs Direct Test, positive Thrombocytopenia*	Hypoprothrombinaemia	Coagulopathy*
Immune system disorders[2]		Hypersensitivity		Anaphylactic shock* Anaphylactic reaction* Anaphylactoid reaction (including shock)*
Vascular disorders		Infusion Site Phlebitis	Haemorrhage*	Shock*
Gastrointestinal disorders		Diarrhoea	Vomiting* Nausea	Pseudomembranous colitis*
Hepatobiliary disorders[3]		Aspartate aminotransferase increased Alanine aminotransferase increased Blood alkaline phosphatase increased Jaundice*		
Skin and subcutaneous tissue disorders		Pruritus* Urticaria Rash maculopapular		Toxic epidermal necrolysis* Stevens Johnson Syndrome* Dermatitis exfoliative*
Renal and urinary disorders				BUN and serum creatinine increased (transient)

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Not known
General disorders and administration site conditions		Administration site pain	Drug fever, Pyrexia	Headache Sensation of cold

[1] Associated with prolonged administration, reversible.
[2] More likely to occur in patients with a history of allergies, particularly to penicillin.
[3] Mostly mild or moderate in severity.
* ADR identified post-marketing

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing 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 according to their local country requirements.

4.9 Overdose

Limited information is available on the acute toxicity of cefoperazone in humans. Overdosage of the drug would be expected to produce manifestations that are principally extensions of the adverse reactions reported with the drug in section 4.8. The fact that high cerebral spinal fluid concentrations of beta-lactam antibiotics may cause neurologic effects and the potential for seizures should be considered.
Since cefoperazone is removed from the circulation by hemodialysis, this procedure may enhance the elimination of the drug from the body should overdosage occur in some patients with impaired renal function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Antiinfectives for systemic use, Third-generation cephalosporins; ATC-Code J01DD12

Mechanism of action
Cefoperazone is a semisynthetic broad-spectrum cephalosporin with a bactericial action, which results from the inhibition of bacterial cell wall synthesis. Like all cephalosporins, Cefoperazone selectively blocks peptidoglycan synthesis by binding to cell receptors (penicillin binding proteins) and inhibiting the transpeptidase reaction.

Cefoperazone is *in vitro* active against a wide variety of clinically significant organisms, and is resistant to degradation by many betalactamases.

Cefoperazone has rapid bactericidal activity, which is concentration-dependent, against susceptible Gram positive and Gram negative organisms in vitro. In infected animal models, AUC/MIC and Cmax/MIC were the PK/PD drivers for efficacy.

Mechanism of resistance
Bacterial resistance to cefoperazone may be due to one or more of the following mechanisms:
- hydrolysis by beta-lactamases. Cefoperazone may be efficiently hydrolyzed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably depressed in certain aerobic Gram-negative bacterial species.
- reduced affinity of penicillin-binding proteins for cefoperazone, e.g. PBP2A in methicillin-resistant *Staphylococcus aureus*.
- outer membrane impermeability, which restricts access of cefoperazone to penicillin-binding proteins in Gram-negative organisms.

- bacterial efflux pumps

Breakpoints
The MIC breakpoints established by Clinical and Laboratory Standards Institute (CLSI) are:
Enterobacteriaceae: S ≤16 mg/L and R ≥64 mg/L
Staphylococcus: S ≤16 mg/L and R ≥64 mg/L
Pseudomonas aeruginosa: S ≤16 mg/L and R ≥64 mg/L

Sensitivity of microorganisms
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic grampositive organisms
Staphylococcus aureus (methicillin-susceptible)
Staphylococcus epidermidis (methicillin-susceptible)
Streptococcus pneumoniae (formerly *Diplococcus pneumoniae)*
Streptococcus pyogenes (Group A beta-hemolytic streptococci)
Streptococcus agalactiae (Group B beta-hemolytic streptococci)
Beta-hemolytic streptococci
Aerobic gramnegative organisms
Citrobacter spp.
Haemophilus influenzae (β-Lactamase positive and negative strains)
Escherichia coli
Klebsiella pneumoniae
Morganella morganii (formerly *Proteus morganii*)
Neisseria gonorrhoeae
Neisseria meningitidis
Proteus mirabilis
Providencia rettgeri (formerly *Proteus rettgeri)*
Providencia spp.
Pseudomonas aeruginosa
Salmonella spp.
Shigella spp.
Serratia spp. (including *S. marcescens)*
Yersinia enterocolitica
Anaerobic grampositive microorganisms
Clostridium spp. (except for *Clostridium difficile)*
Eubacterium spp.
Lactobacillus spp.
Peptococcus spp.
Peptostreptococcus spp.
Anaerobic gramnegative microorganisms
Bacteroides fragilis
Bacteroides spp.
Fusobacterium spp.
Veillonella spp.
Species for which acquired resistance may be a problem
Aerobic grampositive microorganisms

Enterococcus spp.
Streptococcus pneumoniae (penicillin-resistant*)*
Aerobic gramnegative microorganisms
Acinetobacter spp.
Bordetella pertussis
Citrobacter freundii
Enterobacter spp.
Klebsiella oxytoca
Proteus penneri
Proteus vulgaris
Proteus spp.
Inherently resistant microorganisms
Aerobic grampositive microorganisms
Enterococcus spp.
Listeria monocytogenes
Staphylococcus aureus (methicillin-resistant)
Coagulase negative Staphylococci (methicillin-resistant)
Aerobic gramnegative microorganisms
Stenotrophomonas maltophilia

5.2 Pharmacokinetic properties

Distribution
Both after intravenous and intramuscular administration, a dose-proportional increase in plasma concentrations is seen; peak plasma levels are reached within 1 - 2 hours after intramuscular administration. Plasma protein binding of cefoperazone is 90%, the volume of distribution is 0.15 l/kg body weight. Therapeutic concentrations are reached in e.g. cerebrospinal fluid (especially in patients with inflamed meninges), peritoneal fluid, sputum, bile, urine, tonsils, sinus mucous membrane, cardiac muscle, lungs, gallbladder wall, kidneys, prostate, testis, uterus, fallopian tubes, bones. Cefoperazone crosses the placental barrier, therapeutic concentrations being reached in umbilical cord blood and amniotic fluid.

Biotransformation and elimination
Independent of the route of administration, the mean serum half-life is approximately 2 hours. Most part of cefoperazone is excreted in the bile (maximum bile concentrations are reached within 1 - 3 hours after administration), 20 - 30% by the urine in individuals with normal renal function; less than 1% of cefoperazone is metabolised.
Due to its extensive biliary excretion, there are no essential changes of the pharmacokinetics in patients with renal impairment. In patients with hepatic insufficiency and/or biliary obstruction, however, serum half-life may be prolonged and relative excretion by the urine increased.

5.3 Preclinical safety data

Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1000 mg/kg/day (approximately 16 times the average adult human dose) resulted in reduced testicular weight, arrested spermatogenesis, reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range; the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically, the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Cefoperazone is only compatible with the solutions mentioned in section 6.6.
Cefoperazone is incompatible with aminoglycosides; the two drugs must not be mixed nor injected at the same time or at the same site. The solutions should be prepared shortly before injection. (See also section 4.2). The reconstituted solution is chemically and physically stable at 15° C to 25° C for 24 hours. Or 5 days in a temperature (2-8) C or for 21 days under the condition to be stored in refrigerator in -10 C to -20 using sterile water for injection .

Reconstituted CEFOBID solutions may be stored in plastic syringes, or in flexible plastic parenteral solution containers.
Frozen samples should be thawed at room temperature before use. After thawing, unused portions should be discarded. Do not refreeze.

6.3 Shelf life

Do not use CEFOBID after the expiry date which is stated on the Vial label after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Keep out of the sight and reach of children.
See outer carton box
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Cefobid is available as powder for solution for injection& infusion in 0.5 g ,1.0 g and 2 gm powder in clear glass (type III) vials Cefobid 0.5 g : Pack contains 1 vial + 1 ampoule of 5 ml water for injection & an inner leaflet.
Cefobid 1 g: Pack contains 1 vial + 2 ampoules each of 5 ml water for injection & an inner leaflet
Cefobid 2 g: Pack contains 1 vial + 2 ampoules each of 5 ml water for injection & an inner leaflet

6.6 Special precautions for disposal and other handling

For single use only. Only clear solutions should be used immediately after reconstitution.
The following parenteral diluents and CEFOBID are compatible
5% Dextrose Injection
5% Dextrose and Lactated Ringer's Injection
5% Dextrose and 0.9 Sodium Chloride Injection
5% Dextrose and 0.2% Sodium Chloride Injection
10% Dextrose Injection
Lactated Ringer's Injection
0.5% Lidocaine Hydrochloride Injection
0.9% Sodium Chloride Injection

Sterile Water for Injection

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

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Cefobid 0.5 and 1 gm: Pfizer Inc. USA.

Cefobid 2 gm: Pfizer Egypt.

MANUFACUTRED, PACKED & RELEASED BY

SmithKline Beecham- Egypt under license Pfizer Inc. USA.

8. PRESCRIPTION STATUS

Subject to non-repeatable medical prescription, available at pharmacies only

9. DATE OF REVISION OF THE TEXT

April 2017

To Report any side effect:

Pharmacovigilance center, Pfizer Pharmaceutical Company: EGY.AEReporting@pfizer.com

Egyptian Pharmacovigilance center (EPVC), EDA: pv.report@edaegypt.gov.eg

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers

Union of Arabic Pharmacists