1. NAME OF THE MEDICINAL PRODUCT
Peflovin Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Pefloxacin Mesylate Dihydrate equivalent to Pefloxacin 400 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet.

White coloured capsule shaped biconvex film coated tablet embossed "PEV" on one side and "AVRO" on the reverse side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Pefloxacin is indicated for the treatment of single or mixed infections caused by two or more susceptible organisms. It can also be used for infections caused by organisms resistant to other antibiotics including aminoglycoside, penicillin and cephalosporin.

Pefloxacin is indicated for the treatment of the following infections caused by sensitive bacteria.

Severe systemic infection: Septicaemia, bacteraemia, peritonitis, infections in immunosuppressed patients with haematological or solid tumors and in patients in intensive care unit with specific problems such as infected burns.

Urinary tract infection: Uncomplicated and complicated urethritis, cystitis, pyelonephritis, prostatitis, epididymitis.
Respiratory tract infection : Lobar and bronchopneumonia, acute and chronic bronchitis, acute exacerbation of cystic fibrosis, bronchiectasis, empyema.

Gastrointestinal infection: Enteric fever, infective diarrhoea.

Infections of the biliary system: Cholangitis, cholecystitis, empyema of the gall bladder.

Skin and soft tissue infection: Infected ulcers, wound infections, abscesses, cellulitis, otitis externa, erysipelas, infected burns.

Eye, ear, nose and throat infection: Otitis media, sinusitis, mastoiditis, tonsillitis.

Intra-abdominal infection: Peritonitis, intra-abdominal abscesses.

Bone and joint infection: Osteomyelitis, septic arthritis.

Pelvic infection: Salpingitis, endometritis, pelvic inflammatory diseases.

Gonorrhoea: Including urethral, rectal and pharyngeal gonorrhoea caused by β lactamase producing organisms or organisms moderately sensitive to penicillin.

4.2 Posology and method of administration
Posology

Adults:
Standard Dose:

Adults: The usual dose is 400 mg twice daily (morning and evening) by mouth in most infections.

Gonococcal urethritis (in men) & acute uncomplicated cystitis (in women):
A single oral dose of 800mg.

Dosage should be adjusted for adults with hepatic insufficiency. Patients should take the drug with meals to avoid gastrointestinal disturbances.

Children: Not recommended.

Method of administration
Caplets are to be swallowed whole and unchewed with fluid. It is recommended that the caplets be taken during or after a meal. Patients should be advised to drink plenty of fluid. The caplets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).
In severe cases or if the patient is unable to take caplets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications
Peflovin is contraindicated in persons with a history of hypersensitivity to pefloxacin or any member of the quinolone and fluoroquinolone class of antimicrobial agents

It is also contra-indicated in pre-pubertal children, growing adolescents, and pregnant women, nursing mothers and in patients with glucose-6-phosphate dehydrogenase deficiency except where the benefits outweigh the risks. Experimental evidence indicates that species variable reversible lesions of the cartilage of weight-bearing joints (arthropathy) has been seen in immature members of certain animal species.

It is contraindicated in patients on Theophylline, Caffeine, or a Nonsteroidal anti-inflammatory drug therapy.

Paediatric population
The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.4 Special warnings and precautions for use
Pefloxacin should be used with caution in patients with a history of convulsive disorders.

Avoid exposure to sunlight and ultraviolet radiation during treatment with Pefloxacin and for a few days afterwards because of the risk of photosensitivity reactions.

Dosage readjustment is required in severe hepatic insufficiency.

Crystalluria has occurred with large doses, thus patients are advised to maintain an adequate intake of fluid during treatment with Pefloxacin.

Peflovin should be discontinued at the first sign of rash or any other hypersensitivity reaction. Limited evidence suggests that the frequency of severe hypersensitivity reactions may be higher in patients with Acquired Immuno deficiency Syndrome (AIDS) than in other patients

Pefloxacin is associated with an increased risk of tendinitis and tendon rupture and peripheral nerve damage. Discontinue use if symptoms occur and consult your physician.

As Streptococcus Pneumoniae and other Streptococci are not consistently sensitive to Pefloxacin, should not be prescribed as the initial treatment in respiratory infections when a bacteriological examination has not been carried out.

4.5 Interaction with other medicinal products and other forms of interaction

METHYLXANTHINES
As with other quinolones, concurrent administration of pefloxacin with theophylline results in inhibition of theophylline metabolism and may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate. Pefloxacin also interferes with the the metabolism of caffeine by inhibiting the formation of paraxanthine after caffeine administration. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life, resulting in toxicity from elevated serum concentrations.

WARFARIN
Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin and its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

PROBENICID
Probenicid interferes with renal tubular secretion of pefloxacin and produces an increase in the level of pefloxacin in the serum. This should be considered if the patients are receiving both drugs concomitantly.

ANTACIDS
Concurrent administration of pefloxacin with antacids containing magnesium, aluminium, or calcium; with sucralfate or divalent and trivalent cations such as iron may substantially interfere with the absorption of pefloxacin , resulting in serum and urine levels considerably lower than desired. To a lesser extent this effect is demonstrated with zinc-containing multivitamins.

CYCLOSPORINE
Some quinolones, including pefloxacin, have been associated with elevations in serum creatinine clearance in patients receiving cyclosporine concomitantly.

PHENYTOIN
Altered levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant pefloxacin.

SULFONYLUREAS (GLYBURIDE)
The concomitant administration of pefloxacin with the sulfonylurea glyburide, has on rare occasions, resulted in severe hypoglycaemia.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)
Concurrent administration of a NSAID may potentiate CNS stimulant effect of pefloxacin with seizures reported in patients receiving enoxacin and fenbufen.

ANTINEOPLASTIC DRUGS
Decrease serum levels of pefloxacin.

RIFAMPICIN

Decreases serum concentration of pefloxacin

CHLORAMPHENICOL
Antagonises effects of pefloxacin.

4.6 Fertility, pregnancy and lactation
Pregnancy:
While there are no controlled studies of pefloxacin use in pregnant women to show safety, an expert review of published data on experiences with pefloxacin use during pregnancy by TERIS – The Teratogen Information System, concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk. However, there are no human data available to assess the effects of long-term therapy in pregnant women such as that proposed for the treatment of anthrax exposure.

The association between fluoroquinolones and arthropathy, although observed in immature animals and rarely reported in humans, has resulted in the restricted use of fluoroquinolones during pregnancy.

Breast-feeding:
Pefloxacin is excreted into breast milk but is considered as "usually compatible with breastfeeding" by the American Academy of Paediatrics.

4.7 Effects on ability to drive and use machines
Due to its neurological effects, Pefloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.
If any abnormal neurological signs develop during Peflovin therapy, the drug should be discontinued.

4.8 Undesirable effects
Reported side effects have generally been infrequent, mild and self-limiting.
Side effects may include stomach upset, loss of appetite, diarrhoea, nausea, vomiting, insomnia, headache or dizziness, visual and other sensory disturbances and infrequently drowsiness during the first days as the patient's body adjusts to the medication.

Allergic reactions may also occur, symptoms of allergic reactions include: rash, itching, swelling, fever, difficulty in breathing. It also may also affect the musculoskeletal system (muscle and/or joint pain).

Blood disturbances like eosinophilia, leucopenia and thrombocytopenia may also occur.

Adverse reactions are rare and usually abate with discontinuation of the drug. They include; vision changes, nervousness, insomnia, nausea, headache, abdominal pain or discomfort. Rarely, hallucinations, delirium, and seizures have occurred, predominantly in patients who were receiving theophylline or an NSAID. Rashes, including photosensitivity reactions, also can occur. Arthropathy can be produced in several species of immature animals. Arthralgias and joint swelling have developed in children receiving fluoroquinolones. Other reactions that may occur are; agitation, allergic reactions, angioedema, confusion, difficulty in breathing, erythema, interstitial nephritis, psychoses, Steven-Johnson syndrome, tendonitis and tremor.

Crystalluria has occurred with large doses, thus patients are advised to maintain an adequate intake of fluid during treatment with pefloxacin. Leukopenia and oesinophilia and mild elevation in serum transaminases rarely occur.

If these symptoms persist or become more severe, inform your doctor

4.9 Overdose
Symptoms
Adverse reactions include peripheral neuropathy, nervousness, agitation, anxiety, and phototoxic events (rash, itching, burning) due to sunlight exposure.

Management
In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. It is recommended to monitor renal function and to administer Magnesium or Calcium-containing antacids which reduce the absorption of pefloxacin. Less than 10% is removed from the body after haemolysis or peritoneal dialysis. Treatment should be symptomatic and supportive.

ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pefloxacin is a fluorinated 4-quinolone antimicrobial agent with a similar antibacterial spectrum with norfloxacin but greater activity.

As antibacterial concentrations of pefloxacin are obtained in serum and body tissues as well as in the urine following oral administration, pefloxacin has been suggested for use in the treatment of a wide range of infections caused by susceptible organisms. MICs for susceptible Gram-negative aerobic organisms range from 0.004 to 2µg per mL and for Gram-positive organisms from 0.12 to 4µg per mL.

Mechanism of Action
Pefloxacin has been shown to be bactericidal with the MIC (minimum inhibitory concentration) close to the MBC and to act by inhibiting the A subunit of the bacterial enzyme DNA gyrase (topoisomerase), which catalyses the supercoiling necessary to pack DNA into bacterial cells. Its inhibition leads to irreversible chromosome damage and cell death. A secondary action on cell membranes may also contribute to their bactericidal action.

Mechanism of resistance
Resistance can be induced as can cross-resistance between the 4-quinolones, although it has been considered unlikely that such resistance would diminish any clinical effect since the increased MICs are still within achievable concentrations in vitro.

The 4-quinolones are broad-spectrum antibiotics for which plasmid-mediated resistance has not yet been identified. Bacteria are able to develop resistance to these drugs via chromosomal mutations which result in an altered target (DNA gyrase) or reduced uptake of the drug (associated with alterations in the outer membrane). Resistance to the 4-quinolones has been shown to occur clinically but its occurrence is still relatively infrequent. However, the incidence of resistance appears to be increasing in certain groups such as staphylococci and pseudomonads. It is to be hoped that, with appropriate use and dosing, the incidence of resistance to the modern fluorinated 4-quinolones will remain relatively low in the near future.

Spectrum of antibacterial activity
Susceptible organisms include:

Gram-negative organisms:
Escherichia coli, Citrobacter, Enterobacter, Klebsiella, Proteus, Salmonella, Shigella, and *Yersinia* spp. *Pseudomonas aeruginosa*, other *Pseudomonas* spp., (but to a lesser degree). *Haemophilus influenzae, Neisseria gonorrhoeae*, and *Acinetobacter* spp., *Campylobacter, Providencia, Serratia*, and *Legionella* spp.

Chlamydia trachomatis, Moraxella catarrhalis (Branhamella catarrhalis), *Gardnerella vaginalis, Mycoplasma hominis,* and some *Mycobacterium* spp.

Gram-positive:
Staphylococci, Streptococci, and *Listeria* spp.

Anaerobic organisms:
Bacteroides and *Clostridium* spp. may be susceptible or they may not.

Other organisms:
Methicillin-resistant staphylococci and Streptococci pneumoniae resistant to other antibiotics. Pefloxacin has bactericidal activity against Mycobacterium leprae.

5.2 Pharmacokinetic properties

ABSORPTION
Pefloxacin is rapidly and well absorbed after oral administration with a bioavailability of 70%. A 500mg oral dose produces a mean peak plasma concentration of about 2.5µg per mL after 1 to 2 hours. Food does not impair oral absorption, but may delay the time to peak serum concentrations.

DISTRIBUTION
The volume of distribution of pefloxacin is high (approximately 300L), this is well above the extravascular volume indicating extensive tissue penetration in therapeutic concentrations. Pefloxacin is present in the lung, skin, fat, muscle, cartilage, and bone. It is also present in the active form in the saliva, nasal, and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile secretions, prostatic secretions, cerebrospinal fluid and the aqueous humour. The concentrations of the drug in urine, kidney, lung and prostate tissue, stool, bile, macrophages, and neutrophils are higher than serum levels. Pefloaxcin concentrations in the cerebrospinal fluid and prostatic fluid are lower than in the serum. Plasma protein binding is low; figures vary but range from 20 to 40%. Pefloxacin crosses the placenta and is distributed into the amniotic fluid in humans. It is also excreted in breast milk; concentrations were higher than concomitant serum concentrations for up to 12 hours after a dose.

METABOLISM
Pefloxacin is has a plasma half-life of 8 to 13 hours and is extensively metabolized, the main metabolite being N-desmethylpefloxacin.

EXCRETION
About 30 to 50% of an oral dose of pefloxacin is excreted in the urine within 24 hours as unchanged drug and biologically active metabolites. Peak urinary concentrations ranging from about 300 to 500ug per mL have been achieved after a 500mg oral dose. Renal clearance is approximately 300mL per minute. Dose adjustments in patients with renal insufficiency are thus required. Significant amounts of an oral dose appear in the faeces (faecal elimination is about 25% of oral dose). The elimination half-life of unchanged pefloxacin is about 3.5 to 4.5 hours though it may be prolonged in renal insufficiency and in the elderly. The elimination kinetics are linear; after repeated dosing at 12 hourly intervals and once steady state has been reached, no accumulation occurs. Pefloxacin is not effectively removed by peritoneal or haemodialysis.

5.3 Preclinical safety data
Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, pefloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability
As reported for other gyrase inhibitors, pefloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, pefloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet Core:
Pefloxacin Mesilate, Maize Starch, Povidone K.30, Isopropyl Alcohol, Avicel PH 101
Magnesium Stearate, Talc Powder
Film Coating:
Instacoat White

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Product should be stored below 30^{o}C and protected from light.

6.5 Nature and contents of container
Transparent colourless PVC/Aluminium blister. Pack sizes of 10 caplets.

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

7. APPLICANT/MANUFACTURER
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