SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT
   Nalidixic Acid 500 mg

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
   Nalidixic Acid BP 500.00 mg

3  PHARMACEUTICAL FORM
   Tablets

4  CLINICAL PARTICULARS

4.1  Therapeutic indications
   For the treatment of acute or chronic infections, especially those of the urinary tract caused by Gram-negative organisms, other than pseudomonas species, sensitive to Nalidixic Acid. It may also be used for the treatment of gastrointestinal gram-negative infections sensitive to Nalidixic Acid where appropriate, though relapse rate and treatment failure in gastrointestinal infection may be more common.

4.2  Posology and method of administration
   For oral administration only. Nalidixic acid should be taken on an empty stomach, preferably one hour before a meal.

   Adults (including the elderly):

   For acute infections 1 g four times daily for at least seven days, reducing to
0.5 g four times a day for chronic infections.

*Children over 3 months:*

Oral suspension is recommended.

The maximum recommended dose is 50 mg/kg bodyweight per day, in divided doses. Where prolonged treatment is necessary it may be possible to reduce the dose to 30 mg/kg bodyweight without loss of therapeutic benefit.

*Patients with renal-failure:*

The normal dose of nalidixic acid may be employed in patients with creatinine clearance of more than 20 ml/minute. Dosage should be halved in patients with creatinine clearance of 20 ml/minute or less.

### 4.3 Contraindications

Nalidixic Acid is contraindicated for infants less than 3 months of age and patients with a history of convulsive disorders, porphyria or hypersensitivity to Nalidixic Acid or related compounds.

### 4.4 Special warnings and precautions for use

Particular caution is advised in patients with a known allergic disposition.

Nalidixic Acid is mainly metabolised by the liver and should therefore be used with caution in patients with liver disease. Care should be exercised in treating patients with renal failure; the normal dose of Nalidixic Acid may be administered to patients with creatinine clearance of more than 20 ml/minute but dosage should be halved in patients with creatinine clearance of 20 ml/minute or less.

Patients taking Nalidixic Acid should avoid excessive exposure to sunlight (including sunbathing).

Caution should be observed in patients with severe cerebral arteriosclerosis or glucose-6-phosphate dehydrogenase deficiency.

When Nalidixic Acid is given to patients on anticoagulant therapy, it may be necessary to reduce the anticoagulant dosage.

Nalidixic Acid has been shown to induce lesions in weight-bearing joints of young animals. The relevance of this to man is unknown. The possible risk of
late degenerative joint changes in young patients receiving Nalidixic Acid preparations should therefore be considered. If symptoms of arthralgia occur, treatment with Nalidixic Acid should be stopped.

Not recommended for infants less than 3 months of age (see section 4.3).

Caution should be observed and therapy discontinued if patients develop signs or symptoms suggestive of an increase in intracranial pressure, psychosis or other toxic manifestations.

Blood count; renal and liver function should be monitored periodically if treatment is continued for more than two weeks.

If the clinical response is unsatisfactory or if relapse occurs, therapy should be reviewed in the light of appropriate culture and sensitivity tests. If bacterial resistance to nalidixic acid develops it does so usually within 48 hours. Cross-resistance between nalidixic acid and other quinolone derivatives such as oxolinic acid and cinoxacin have been observed.

4.5 Interaction with other medicinal products and other forms of interaction

Nalidixic Acid may interact with anticoagulants due to competition for protein binding sites and it may therefore be necessary to reduce the anticoagulant dosage and monitor the prothrombin time during coadministration, until a satisfactory prothrombin ratio is achieved.

There have been reports of serious gastrointestinal toxicity following concomitant use of nalidixic acid and melphalan.

Nalidixic Acid in therapeutic doses can interfere with the estimation of urinary 17-ketosteroids and may cause high results in the assay of urinary vanilmandelic-acid (Pisano method).

When testing for glycosuria in patients receiving Nalidixic Acid, glucose-specific methods based on glucose oxidase should be used because copper reduction methods may give false-positive results.

Active proliferation of the organisms is a necessary condition for the antibacterial activity of Nalidixic Acid: the action of Nalidixic Acid may therefore be inhibited by the presence of other antibacterial substances, especially bacteriostatic agents such as tetracycline, chloramphenicol and nitrofurantoin which is antagonistic to Nalidixic Acid in vitro.

Nalidixic Acid also interacts with probenecid, which inhibits the tubular secretion of Nalidixic Acid. This may reduce the efficacy of the product in the treatment of urinary tract infections.
It is possible that there will be increased risk of nephrotoxicity with ciclosporin.

4.6 Pregnancy and lactation
Although there is no evidence that Nalidixic Acid has any harmful effect during pregnancy, careful consideration should be given to its use during the first trimester. When treating women who are breast feeding, consideration should be given to the fact that traces of Nalidixic Acid are excreted in the milk.

4.7 Effects on ability to drive and use machines
No specific warning.

4.8 Undesirable effects
Reactions reported after oral administrations of Nalidixic Acid include CNS side effects: Drowsiness, weakness, headache, dizziness and vertigo.

Reversible subjective visual disturbances without objective findings have occurred infrequently (generally with each dose during the first few days of treatment). These reactions include overbrightness of lights, change in colour perception, difficulty in focusing, decrease in visual acuity, and double vision. They usually disappeared promptly when dosage was reduced or therapy was discontinued.

Toxic psychosis or brief convulsions have been reported rarely, usually following excessive doses. In general, the convulsions have occurred in patients with predisposing factors such as epilepsy or cerebral arteriosclerosis.

In infants and children receiving therapeutic doses of Nalidixic Acid, increased intercranial pressure with bulging anterior fontanelle, papilloedema, and headache have occasionally been observed. A few cases of 6th cranial nerve palsy have been reported. Although the mechanisms of these reactions are unknown, the signs and symptoms usually disappeared rapidly with no sequelae when treatment was discontinued.

Gastrointestinal: Abdominal pain, nausea, vomiting and diarrhoea.

Allergic: Rash, pruritus, urticaria, angio-oedema, eosinophilia, arthralgia with joint stiffness and swelling, and rarely, anaphylactoid reaction.
Photosensitivity reactions consisting of erythema and bullae on exposed skin surfaces usually resolve completely in 2 weeks to 2 months after Nalidixic Acid is discontinued; however, bullae may continue to appear with successive exposures to sunlight or with mild skin trauma for up to 3 months after discontinuation of the drug (see 4.4.).

Other: Rarely cholestasis, parathaesia, metabolic acidosis, thrombocytopenia, leukopenia, or haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

4.9 Overdose
In adults, symptoms of overdosage have been noted following single doses of 20 and 25 g. These have included toxic psychosis and convulsions. Occasional reports of metabolic acidoses have occurred in association with overdosage, use in infants under the age of 3 months, or overdose with concurrent use of probenecid.

In an emergency, it is suggested that the stomach should be emptied, and symptomatic treatment applied as necessary, a particular watch being kept for central or respiratory depression.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Nalidixic acid is bactericidal and inhibits gram-negative micro-organisms, including Escherichia coli, Klebsiella aerogenes, Kleb. pneumoniae, Salmonella spp., Shigella spp., and Proteus spp. Brucella spp. may be sensitive. Minimum inhibitory concentrations are reported to range from about 5 to 75 µg per ml. Many organisms are inhibited by 10 µg per ml or less. Pseudomonas aeruginosa is usually resistant. Bacterial resistance may develop rapidly, sometimes within a few days and cross-resistance with oxolinic acid occurs.

Antibacterial activity of nalidixic acid is not significantly affected by differences in urinary pH.
5.2 Pharmacokinetic properties
Nalidixic acid is readily absorbed from the gastrointestinal tract. The plasma half-life is about 90 minutes and peak plasma concentrations of 20 to 50 μg per ml have been reported 2 hours after the administration of 1 g by mouth. About 90% of the drug is bound to plasma proteins.

It is rapidly metabolised, mainly to hydroxy-nalidixic acid which also has antibacterial activity and accounts for about 30% of active drug in the blood. About 80% of a dose appears in the urine within 8 hours, most of the nalidixic acid and its active metabolite having been conjugated in the liver to inactive glucuronides but urinary concentrations of free drug and active metabolite ranging from 25 to 250 μg per ml are achieved after a single 1 g dose. Hydroxynalidixic acid accounts for about 85% of this activity.

Only traces of nalidixic acid appear in milk and cerebrospinal fluid. About 4% of a dose is excreted in the faeces.

5.3 Preclinical safety data
Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose
Maize starch
Povidone
Sodium starch glycollate
Iron oxide E172
Magnesium stearate
Purified water

6.2 Incompatibilities
None known.
6.3 Shelf life

48 months all pack sizes.

6.4 Special precautions for storage
Store below 25°C in a dry place. Keep container well closed.

6.5 Nature and contents of container
High density polystyrene containers with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane or polythene wads.

Pack sizes: 56, 100, 112, 500, 1000

6.6 Special precautions for disposal
No special instructions.

7 MARKETING AUTHORISATION HOLDER

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NICOSIA
CYPRUS
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CYPRUS

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