SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

HANCLARO-500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Clarithromycin USP….

3. PHARMACEUTICAL FORM

White colored, round shaped film coated tablets, scored on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HANCLARARO-500 (Clarithromycin) is indicated for treatment of infections due to susceptible organisms. Such infections include:
Lower respiratory tract infections (e.g., bronchitis, pneumonia)
Upper respiratory tract infections (e.g., pharyngitis, sinusitis, tonsillitis)
Acute otitis media in children
Skin and soft tissue infections (e.g., folliculitis, cellulitis, erysipelas)
Leprosy
Disseminated or localized mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localized infections due to *Mycobacterium chelonae*, *Mycobacterium fortuitum*, or *Mycobacterium kansasii*.
It is also used in some countries as an alternative to penicillins for prophylaxis of endocarditis.
To eradicate *Helicobacter pylori* in treatment regimens for peptic ulcer disease. It has been tried in protozoal infections, including toxoplasmosis.
Clarithromycin tablets and granules for oral suspension are indicated for the prevention of disseminated Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection.

4.2 Posology and method of administration

Adults:
The usual recommended dosage of HANCLARARO-500 (Clarithromycin) is one 250mg tablet twice daily. In more severe infections the dosage can be increased to 500mg twice daily. The usual duration of therapy is 7 to 14 days.

HANCLARARO-500 (Clarithromycin) suspension may be used as an alternative dosage form for those adults that prefer a liquid medicine.
The following table is a suggested guide for determining dosage.

Adult Dosage Guidelines		
Infection	**Dosage (q12h)**	**Normal Duration (days)**
Pharyngitis/Tonsillitis	250mg	10
Acute maxillary sinusitis	500mg	14
Acute exacerbation of chronic bronchitis due to:		
S. pneumoniae	250mg	7 to 14
M. catarrhalis	250mg	7 to 14
H. influenzae	500mg	7 to 14
Pneumonia due to:		
S. pneumoniae	250mg	7 to 14
M. pneumoniae	250mg	7 to 14
Uncomplicated skin and skin structure	250mg	7 to 14

Children:
The usual recommended daily dosage of HANCLARARO-500 (Clarithromycin) is 7.5mg/kg/day up to a maximum of 500mg twice daily. The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition. The following table is a suggested guide for determining dosage.

Pediatric Dosage Guidelines (Based on Body Wt.)		
Weight*	**Dosage in mg**	**Dosage in mL 125mg/5mL**
	Given twice daily	
8-11 kg (1-2 yrs)**	62.5mg	2.5mL (1/2 tsp. b.i.d.)
12-19 kg (3-6 yrs)	125mg	5mL (1 tsp. b.i.d.)
20-29 kg (7-9 yrs)	187.5mg	7.5mL ($1^{1/2}$ tsp. b.i.d.)
30-40kg (10-12 yrs)	250mg	10mL (2 tsp. b.i.d.)
* Children < 8kg should be dosed on a per kg basis (approx 7.5mg/kg BID) * Approximate ages		

Dosage for the eradication of H. pylori associated with peptic ulcer disease
HANCLARARO-500 (Clarithromycin), usually in a dose of 500mg twice daily, is given with another antibacterial and either a proton pump inhibitor or a histamine H_2-receptor antagonist, for 7 to 14 days.

Dosage for Mycobacterial Infections
In children with disseminated or localized mycobacterial infections *(M.avium, M. Intracellulare, M. chelonae, M.fortuitum, M. kansasii*), the recommended dose is 7.5 to 15mg/kg clarithromycin twice daily.
Treatment of disseminated MAC infections in AIDS patients should be continued as long as clinical and microbiological benefit is demonstrated. Treatment of other mycobacterial infections should continue at the discretion of the physician. Clarithromycin should be used in conjunction with other antimycobacterial agents. Dosing recommendations for children are in the table below.

Dosage guidelines for pediatric AIDS patients based on body weight

Dosage in mL given twice daily (Clarithromycin 125mg/5mL)		
Weight*	**7.5mg/kg bd**	**15 mg/kg bd**
8-11 kg	2.5mL (1/2 tsp.)	5mL (1 tsp)
12-19 kg	5mL (1 tsp.)	10mL (2 tsp)
20-29 kg	7.5mL ($1^{1/2}$ tsp.)	15mL (3 tsp)
30-40kg	10mL (2 tsp.)	20mL (4 tsp)
* Children < 8 kg should be dosed on a per kg basis (7.5 to 15 mg/kg twice daily)		

***Dosage in renal impairment*:** HANCLARARO-500 (Clarithromycin) may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function. However, in the presence of severe renal impairment (CR_{CL} < 30mL/min), with or without coexisting hepatic impairment, the dose should be halved or the dosing interval doubled. In children with creatinine clearance less than 30mL/min, the dosage of clarithromycin should be reduced by one-half, i.e., up to 250mg once daily, or 250mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.

Directions for Preparing Oral Suspension
Fill drinking water up to the line mark and shake well. The reconstituted suspension can be used for up to 14 days, when stored at the required conditions.

4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs.
Concomitant administration of clarithromycin with any of the following medicines is contraindicated: astemizole, cisapride, pimozide and terfenadine.

4.4 Special warnings and special precautions for use

Caution is required in patients with impaired renal or hepatic function and doses should be reduced in those with severe renal impairment.
Caution should also be paid to the possibility of cross-resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

Pseudomembranous colitis has been reported with nearly all anti-bacterial agents, including macrolides, and may range in severity from mild to life threatening.

Clarithromycin in combination with ranitidine bismuth citrate therapy should not be used in patients with a history of acute porphyria.

4.5 Interaction with other medicaments

Data available to date indicate clarithromycin is metabolized primarily by the hepatic cytochrome P450 3A (CYP3A) isozyme. This is an important mechanism determining many drug interactions.

The metabolism of other drugs by this system may be inhibited by concomitant administration with clarithromycin and may be associated with elevations in serum levels of drug classes known or suspected to be metabolized by the same CYP450 and CYP3A isozyme.

Other Drug Interactions:

Elevated digoxin serum concentrations have been reported in patients receiving clarithromycin tablets and digoxin concomitantly. Monitoring of serum digoxin levels should be considered.

There have been post-marketed reports of *torsades de pointes* occurring with concurrent use of clarithromycin and quinidine or disopyramide. Serum levels of these medications should be monitored during clarithromycin therapy.

Rhabdomyolysis coincident with the co-administration of clarithromycin and the HMG-CoA reductase inhibitors, e.g., lovastatin and simvastatin, has rarely been reported.

Antiretroviral Drug Interactions:

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine.

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200mg q 8 hours and clarithromycin 500mg q 12 hours resulted in a marked inhibition of the metabolism of clarithromycin.

For patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1gm/day should not be co-administered with ritonavir.

4.6 Pregnancy and Lactation

Clarithromycin is excreted into human breast milk therefore clarithromycin should not be used during pregnancy and breast-feeding unless the potential benefit justifies a potential risk to the foetus.
If clarithromycin pediatric suspension is considered for patients of post-pubertal age the physician should carefully weigh the benefits against the risk when pregnancy is either suspected or confirmed.

4.7 Effects on ability to drive and use machine

The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

4.8 Undesirable effects

Clarithromycin is generally well tolerated. The safety profile of the pediatric formulation is similar to that of the 250mg tablet in adult patients.
The most frequently reported side effects of clarithromycin in clinical studies were gastrointestinal related, i.e. nausea, dyspepsia, abdominal pain, vomiting and diarrhea. Other reported side effects include headache, taste perversion and transient elevations of liver enzymes.
Headache and rashes from mild skin eruptions to, rarely, Stevens-Johnson syndrome has occurred. There have also been reports of transient CNS effects such as anxiety, dizziness, insomnia, hallucinations, and confusion.

Other adverse effects include hypoglycemia and thrombocytopenia. Interstitial nephritis, renal failure, hearing loss, glossitis, stomatitis, oral monilia and tongue discoloration have been reported with clarithromycin therapy.

Adverse laboratory changes. Abnormal liver function test results may occur following therapy with clarithromycin. Changes in laboratory parameters without regard to drug relationship are:
Hepatic – elevated SGPT (ALT), SGOT (AST), GGT, alkaline phosphates, LDH, bilirubin.
Hematologic – decreased WBC, platelet count, elevated prothrombin.
Renal - elevated BUN, serum creatinine.

Immunocompromised Pediatric Patients:
In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it is often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or inter-current illness.
The most frequently reported adverse events, excluding those due to the patient's concurrent condition, were tinnitus, deafness, vomiting, nausea, abdominal pain, purpuric rash, pancreatitis and increased amylase. Evaluations of laboratory values for these patients were made by analyzing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. None of these seriously abnormal values for these laboratory

parameters were reported for patients receiving the highest dosage (25mg/kg/day) of clarithromycin.

OVERDOSAGE

Overdosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum concentrations are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

CLINICAL PHARMACOLOGY

Microbiology

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible bacteria and suppresses protein synthesis.

Clarithromycin has demonstrated excellent *in vitro* activity against both standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally one $\log_2$ dilution more potent than the MICs of erythromycin.

Clarithromycin is reported to be more active than erythromycin against susceptible *streptococci* and *staphylococci in vitro*, as well as against some other species including *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Legionella* spp. *Chlamydia trachomatis*, and *Ureaplasma urealyticum*. Clarithromycin is reported to be more active than erythromycin or azithromycin against some mycobacteria, including *Mycobacterium avium* complex, and against *M. leprae*. It is reported to have some *in vitro* activity against the protozoan *Toxoplasma gondii*, and may have some activity against cryptosporidia. The major metabolite 14-hydroxyclarithromycin, is also active, and may enhance the activity of clarithromycin *in vivo*, notably against *Haemophilus influenzae*. *In vitro* data also indicates that clarithromycin has excellent activity against *Legionella pneumophilla*, and *Mycoplasma pneumoniae*. It is bactericidal to *Helicobacter pylori*; this activity of clarithromycin is greater at neutral pH than at acid pH. *In vitro* and *in vivo* data show that this antibiotic has activity against clinically significant mycobacterial species.

5.2 Pharmacokinetic properties

Absorption:

Clarithromycin is rapidly absorbed from G.I tract after oral administration and the bioavailability of the parent drug is about 55%. Food slightly delays the absorption of clarithromycin but does not affect the extent of bioavailability, therefore it may be given without regard to food. Peak concentrations of clarithromycin and its principal active metabolite 14-hydroxyclarithromycin are reported to be about 0.6 and 0.7µg per mL respectively following a single 250mg dose by mouth; at steady state the same dose given

every 12 hours as tablets produces peak concentrations of clarithromycin of about 1µg per mL. The same dose given as a suspension produces a steady-state plasma concentration of about 2µg per mL. The time to peak concentration is about 2-3 hours. The pharmacokinetics of clarithromycin is non-linear and dose dependent; high doses may produce disproportionate increases in peak concentration of the parent drug, due to saturation of the metabolic pathways.

Distribution:
The drug and its principal metabolite are widely distributed, and tissue concentrations exceed those in serum, in part because of intracellular uptake. Volume of distribution is 243-266 Liters.

Metabolism & Excretion:
It is extensively metabolized in the liver and excreted in feces via the bile. Substantial amounts are excreted in urine; at steady state about 20% and 30% of a 250mg or 500mg dose, respectively, is excreted in this way, as unchanged drug. 14-hydroxyclarithromycin as well as other metabolites are also excreted in the urine accounting for 10 to 15% of the dose. The terminal half-life of clarithromycin is reportedly about 3 to 4 hours in patients receiving 250mg doses twice daily, and about 5 to 7 hours in those receiving 500mg twice daily.
The principal metabolite, 14-OH-clarithromycin has an elimination half-life of 5 to 6 hours after a dose of 250mg every 12 hours. With a dose of 500mg every 12 hours, its elimination half-life is about 7 hours. With either dose, the steady-state concentration of this metabolite is generally attained within 2 to 3 days.

Special Populations:
Hepatic Impairment:
The steady-state concentrations of clarithromycin in patients with impaired hepatic function did not differ from those of normal subjects; however, the 14-OH-clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH-clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

Renal Impairment:
The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function who received multiple 500mg oral doses. The plasma levels, half-life C_{max} and C_{min} for both clarithromycin and its 14-OH metabolite were higher and the AUC was larger in subjects with renal impairment than its normal subjects. The extent to which these parameters differed was correlated with the degree of renal impairment; the more severe the renal impairment, the more significant the difference.

Elderly Subjects:
In a comparative study of healthy, young adults and healthy, elderly subjects given multiple 500mg oral doses of clarithromycin, the circulating plasma levels were higher and elimination was slower in the elderly group compared to the younger group. However, there was no difference between the two groups when renal clearance of clarithromycin was

correlated with creatinine clearance. It was concluded from these results that any effect on the handling of clarithromycin is related to renal function and not subject to age.

Patients with Mycobacterial Infections:
Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following administration of usual doses to patients with HIV infections were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations can be much higher than those observed at usual doses. In children with HIV infection taking 15-30mg/kg/day of clarithromycin in two divided doses, steady-state C_{max} values generally ranged from 8 to 20mcg/mL.
However, C_{max} values as high as 23mcg/mL have been observed in HIV-infected pediatric patients taking 30mg/kg/day in two divided doses as clarithromycin pediatric suspension. Elimination half-lives appeared to be lengthened at these higher doses as compared to that observed with usual doses in normal subjects. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose (Avicel PH-102), Lactose Monohydrate, Povidone K-30 (PVP K-30), Croscarmellose Sodium, Colloidal Anhydrous Silica (Aerosil 200), Magnesium Stearate, Hypromellose 5CPS (Methocel E-5), Titanium Dioxide, Macrogols (P.E.G 6000).

6.2 Incompatibilities

None

6.3 Shelf-life

3 Years
The expiration dates refer to the product correctly stored in the required conditions.

6.4 Special precautions for storage

Store below $30^{o}C$
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

6.5 Nature and contents of container

HANCLARARO-500 (Clarithromycin) Tablets are available in Alu-Alu blister pack of 1 x 10 tablets.

6.6 Instructions for use/handling

To be sold on prescription of a registered medical practitioner only.
Keep out of the reach of children.

7. MARKETING AUTHORISATION HOLDER

HANBET PHARMACEUTICAL LIMITED
118, Murtala Mohammed way, Ebute Metta Lagos Nigeria

8. PRODUCT REGISTRATION

NUMBER: B4-3751