Summary of Product Characteristics

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

Trade/Proprietary Name: G-Ciprox™

Approved/Inn/Generic Name: Ciprofloxacin Tablets

1.2 Strength

500mg

1.3 Pharmaceutical form

Tablet

2. Qualitative and quantitative composition

Name of ingredient	**Qty (SI units)**
Ciprofloxacin hydrochloride	500mg(equivalent to Ciprofloxacin)
Magnesium stearate	4mg
Carboxymethyl starch sodium	15mg
PovidoneK-30	12mg

3. Pharmaceutical form

White tablet.

4. Clinical particulars

4.1 Therapeutic indications

Ciprofloxacin is a medicine for the treatment of bacterial infections. Ciprofloxacin is an antibiotic and belongs to the family of quinolones. It has an antibacterial action against a large number of species of bacteria. Ciprofloxacin is suitable for the treatment of infections such as:

Infections of the airways;

Ear, nose and throat infections;

Infections of the mouth, teeth or jaw;

Infections of the kidneys and urinary tract;

Infections of the genital organs;

Infections in gynaecology and obstetrics;

Infections of the gastrointestinal tract;

Infections of the abdominal cavity, including the minor pelvis;

Infections of the skin and soft tissue;

Infections of bones and joints.

Anthrax

For the prevention and treatment of anthrax following inhalation of anthrax bacilli (Bacillus anthracis).The efficacy of Ciprofloxacin in anthrax has been proven in animal experiments.

4.2 Posology and method of administration

Your doctor will decide the dosage and how long your treatment should continue. It is essential to follow your doctor's instructions strictly to derive the maximum benefit from Ciprofloxacin.

Do not stop the therapy prematurely, even if you feel better, because the signs of illness often begin to disappear before the infection has been completely cured.

Not using the medicine for long enough or stopping treatment too early can result in the illness flaring up again.

Ciprofloxacin Tablets are best taken on an empty stomach with a little liquid.

Your doctor will prescribe one of the following dosages depending on the severity of your illness, the sensitivity of the organism causing it and the location of the infection:

Single/daily doses for adults:

Simple infections of the lower and upper urinary tract: 2 x 250 mg. Severe infections of the urinary tract (depending on degree):2 x 250 mg to 2 x 500 mg. Infections of the airways (e.g. bronchitis): 2x250 mg to2x500 mg.

Other infections (see Indications): 2 x 500 mg.

Severe infections (e.g. bone infections, airway infections, or in patients with cystic fibrosis): 3 x 500 mg.

For children and young people (5-17 years old) with cystic fibrosis, the recommended dosage in acute episodes of infection is 2 x 20 mg Ciprofloxacin per kg body weight, divided into 2 single doses at 12-hourly intervals. The daily dose should not exceed 3 x 500 mg. The

recommended duration of treatment is 10-14 days. There is no experience of the dosage for children with impaired kidney or liver function.

In acute, uncomplicated gonorrhoea (clap) in men, a single dose of 250 mg is sufficient if only the urethra is affected. If the symptoms (discharge etc.) in gonorrhoea do not disappear within a few days, your doctor should be consulted to give you a check-up, in particular to rule out a secondary infection which was not cured by the administration of a single dose.

Anthrax

Treatment should be started immediately if the inhalation of anthrax germs is suspected or confirmed.

The prevention or therapy of anthrax is usually started with Ciprofloxacin given as an infusion.

One can then change over to CIPROFLOXACIN TABLETs depending on how the illness progresses.

Adults: 1 CIPROFLOXACIN TABLET 500 mg film-coated tablet x 2 daily.

Children: 15 mg/kg bodyweight x 2 daily.

The maximum single dose for children should not exceed 500 mg.

Duration of treatment: 60 days for the prevention and treatment of infections following inhalation of anthrax germs.
Do not on your own account change the dosage you have been prescribed. If you feel the effect of the medicine is too weak or too strong, talk to your doctor or pharmacist.

4.3 Contraindications

Patients who are hypersensitive to Ciprofloxacin or similar medicines (ask your doctor or pharmacist) must not use CIPROFLOXACIN TABLET.
Children and young people: Children and young people who are still growing should not take CIPROFLOXACIN TABLET. An exception to this is the treatment of acute episodes of infection in patients with cystic fibrosis (a hereditary metabolic disorder with increased production and increased viscosity of the glandular secretions of the bronchi and digestive tract), or with anthrax.

4.4 Special warnings and special precautions for use：

This medicine has been prescribed for you by your doctor to treat your current illness. The antibiotic in CIPROFLOXACIN TABLET is not effective against all micro-organisms that cause infectious diseases. The use of the wrong antibiotic or incorrect dosage of an antibiotic may cause complications. So never use it except on medical advice to treat other illnesses or to treat anyone else.
This medicine may impair your reactions, your ability to drive and to use tools or operate machines. This is especially the case if alcohol is consumed at the same time.
An adequate fluid intake is necessary during treatment with CIPROFLOXACIN TABLET because, otherwise, the active substance may crystallise out in the urine.
If your kidney function is impaired, it maybe necessary to adjust the dosage in some circumstances. Your doctor has the information he needs about this. Patients with known cerebral disease, especially seizures (epilepsy) or disturbed circulation in the brain should only take CIPROFLOXACIN TABLET if they are also receiving treatment for cerebral attacks at the same time.
Excessive exposure to the sun (or time spent in a solarium) should be avoided while under treatment with CIPROFLOXACIN TABLET as sensitive patients may suffer unpleasant reddening of the skin or inflammation (photosensitisation).
In rare cases CIPROFLOXACIN TABLET can cause photosensitivity reactions. Such patients should avoid prolonged exposure to sunlight during therapy with CIPROFLOXACIN TABLET. If this is not possible, a high factor sunscreen cream should be used, and clothing worn to cover the arms and legs, as well as, perhaps, a hat to protect the face.
The simultaneous use of medicines containing iron and medicines for hyperacidity of the stomach containing calcium, aluminium hydroxide or magnesium hydroxide should be avoided as the effect of CIPROFLOXACIN TABLET will be diminished. The same applies to sucralfate, which contains aluminium and is another substance for treating gastric ulcers. CIPROFLOXACIN TABLET should be administered either 1-2 hours before or at least 4 hours after these medicines in order to ensure

adequate absorption by the body.

Please tell your doctor if you are taking blood-thinning preparations (warfarin), theophylline preparations (asthma remedies; the substance is also called aminophylline) at the same time. The side-effects of warfarin and theophylline can sometimes be intensified. Metoclopramide (a medicine for illnesses of the gastrointestinal tract) accelerates the absorption of ciprofloxacin, but this is of no importance as far as the action of this antibiotic is concerned.

If you are taking the medicine glibenclamide to lower your blood sugar at the same time, its effect may be intensified in individual cases, and this can lead to a sugar deficiency.

Taking CIPROFLOXACIN TABLET at the same time as methotrexate, a substance which blocks certain chemical mechanisms in cells and inhibits the growth of specific cells, may increase the effectiveness of methotrexate, and this makes it necessary to monitor the therapy carefully.

Please tell your doctor or pharmacist if you are suffering from other illnesses, if you have allergies or retaking or applying externally any other medicines (including those you have bought yourself!).

4.5 Interactions with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin:

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1 – 2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended.

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.

Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

4.6 Pregnancy and lactation

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals

exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus.
As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The following side-effects can occur when taking CIPROFLOXACIN TABLET:
Gastrointestinal symptoms such as stomach pains, nausea, vomiting,diarrhoea, indigestion, flatulence or loss of appetite. Very rarely:
inflammation of the pancreas. If severe and persistent diarrhoea occurs during or after treatment, you should consult your doctor or pharmacist without delay.
Disturbance of the central nervous system such as dizziness, headache, tiredness, insomnia, agitation or trembling. Very rarely, twitching, disturbed peripheral sensations, increased or diminished sensitivity to touch, tenseness of the muscles, pain in the legs, back or chest, anxiety, nightmares, confusion, depression, sweating, hallucinations, disturbed vision (double vision, seeing colours), unsteadiness when walking, cramps, disturbed sense of taste and smell have been observed.
Skin reactions such as rashes, also in conjunction with severe exposure to the sun. Very rarely: Sudden onset of hypersensitivity reactions, itching, nettle rash, swelling of the face and larynx, shortness of breath, fever. In some cases, a life-threatening state of shock can occur after taking the medicine for the first time. In these cases, CIPROFLOXACIN TABLET must be discontinued immediately; medical treatment is necessary (e.g. treatment for shock). There have been very rare reports of joint pains, muscle pain, inflammation of the sheaths of tendons, general feeling of weakness, palpitations, migraine, hot flushes, fainting, darkening of the skin, bleeding in spots under the skin, blisters forming and filling with blood, small nodules, small nodules with crust formation indicating vascular involvement, inflammation of the kidneys and liver, destruction of liver cells.
Tell your doctor or pharmacist if you notice any symptoms of this sort.
If you notice side-effects which are not described here you should inform your doctor or pharmacist without delay.

4.9 Overdose

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer Mg-or Ca-containing antiacids which reduce the absorption of

ciprofloxacin.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in-vitro mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may affect susceptibility to ciprofloxacin.

Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteria	S ≤ 0.5 mg/L	R > 1 mg/L
Pseudomonas	S ≤ 0.5 mg/L	R > 1 mg/L
Acinetobacter	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp.1	S ≤ 1 mg/L	R > 1 mg/L

Haemophilus influenzae and Moraxella catarrhalis	S ≤ 0.5 mg/L	R > 0.5 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*	S ≤ 0.5 mg/L	R > 1 mg/L

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

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.

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Bacillus anthracis* (1)
Aerobic Gram-negative micro-organisms *Aeromonas* spp. *Brucella* spp. *Citrobacter koseri* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae** *Legionella* spp. *Moraxella catarrhalis** *Neisseria meningitidis* *Pasteurella* spp. *Salmonella* spp.* *Shigella* spp.* *Vibrio* spp. *Yersinia pestis*
Anaerobic micro-organisms

Mobiluncus
Other micro-organisms *Chlamydia trachomatis* ($) *Chlamydia pneumoniae* ($) *Mycoplasma hominis* ($) *Mycoplasma pneumoniae* ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* ($) *Staphylococcus* spp.* (2)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*+ *Burkholderia cepacia*+ * *Campylobacter* spp.+ * *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae** *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*

Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms *Excepted as listed above*
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1 – 2 hours later.

Single doses of 100 – 750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.

The absolute bioavailability is approximately 70 – 80%.

A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20 – 30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2 – 3 L/kg body weight.

Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display in-vitro antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4 – 7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M_1 -M_4)	11.3	7.5

Renal clearance is between 180 – 300 mL/kg/h and the total body clearance is between 480 – 600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6 – 8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7 – 11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8 – 32.0 mg*h/L) and 16.5 mg*h/L (range 11.0 – 23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4 – 5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

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, ciprofloxacin 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, ciprofloxacin 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, ciprofloxacin 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

Magnesium stearate, Carboxymethyl starch sodium, PovidoneK-30

6.2 Incompatibilities

In the absence of compatibility study, this pharmaceutical product must not be mixed with other pharmaceutical products.

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6.3 Shelf life

3 years

6.4 Special precaution for storage

Stored below 30℃, protected from light.

6.5 Nature and contents of container

Aluminiun foil-PVC blister, box, and carton

6.6 Instructions for use and handling <and disposal>

No special requirement.

7. MARKETING AUTHORISATION HOLDER

Guilin Pharmaceutical Co., Ltd.

Address: No.17 Shanghai Road, Guilin, China

Postcode：541002

Tel: 0086-773-3833116

Fax: 0086-773-3832783

Web：http://www.guilinpharma.com

8. MARKETING AUTHORISATION NUMBER(S)

Guilin Pharmaceutical Co., Ltd.

Address: No. 43 Qilidian Road, Guilin, China

Postcode：541004

Tel: 0086-773-3841973

Fax: 0086-773-3841973

Web：http://www.guilinpharma.com

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/07/2014 (DATE OF FIRST AUTHORISATION in Uganda)

10. DATE OF REVISION OF THE TEXT

06/2012