Gatifloxacin for enteric fever

Gatifloxacin for treating enteric fever

Submission to the 18th Expert Committee on the Selection and Use of Essential Medicines
Gatifloxacin for enteric fever

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1 Summary statement of the proposal for inclusion

Enteric fever (Salmonella typhi and S. paratyphi) affects 26 million mostly young people in resource limited setting annually (conservative estimates). Resistance has developed and spread widely against all the traditional treatments and there are few therapeutic options that treat the patient effectively and prevent long term carriage. No antibiotics have ever been developed specifically for the treatment of enteric fever. Very few countries use typhoid vaccines and there is no vaccine for paratyphoid.

Multidrug resistance (MDR = resistance to chloramphenicol, ampicillin and trimethoprim/sulfamethoxazole) and nalidixic acid resistance (reducing the sensitivity to the classical fluoroquinolones ofloxacin and ciprofloxacin) is widespread. Resistance causes higher failure rates and prolonged carriage, increasing the risk of complications in an individual and increasing the potential for continued transmission to the community.

There is good evidence from a series of randomised controlled trials that gatifloxacin can be applied universally in all endemic areas, irrespective of Salmonella susceptibility profiles. There is also pre-clinical and clinical pharmacokinetic/pharmacodynamic (PK/PD) information to support the proposed gatifloxacin treatment.

A once-a-day gatifloxacin 7-day regimen is effective and safe against both sensitive, MDR and nalidixic acid resistant strains of Salmonella typhi and S. paratyphi. No susceptibility screening is required. It is the least expensive treatment currently available.

1.1 Rationale for this submission

The claim is supported by

- In-vitro, clinical (randomised controlled trials, RDTs and meta-analysis) and pharmacological (PK/PD) evidence that gatifloxacin is effective for the treatment of enteric fever, including multi-drug resistant and nalidixic acid resistant strains.
- Safety information based on RDTs of enteric fever and longer exposure for the treatment of tuberculosis.
- Cost and cost-effectiveness data - gatifloxacin is the least expensive option for treating enteric fever.

The product is widely available across disease-endemic countries as a generic product; while approved as a general antibiotic it is not specifically indicated at present for the treatment of enteric fever. However, gatifloxacin has been approved for treating urinary tract infections involving non-Salmonella Enterobacteriaceae, such as Escherichia coli, which is genetically closely related to Salmonella.

2 Focal point in WHO submitting the application

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4 International Nonproprietary Name (INN, generic name) of the medicine

INN: Gatifloxacin
Chemical name: (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate
Molecular formula: C_{19}H_{22}FN_{3}O_{4},11/2H_{2}O =402.4
CAS: 160738-57-8 (anhydrous gatifloxacin); 180200-66-2 (gatifloxacin sesquihydrate)
ATC code: J01MA16; S01AX21
Chemical structure:

5 Formulation proposed for inclusion

Solid oral forms (200mg and 400mg tablets and capsules) are available.
No specific paediatric formulation currently exists.
5.1 Prospective formulation improvements
Ways of stimulating manufacturers to optimize gatifloxacin formulation will be sought. The enteric fever patient population is generally young and small and dosing is based on body weight. While tablet crushing is customary, and a practical dosing schedule is proposed here, smaller (lower strength) tablets, scored tablets or a suspension will improve dosing accuracy.

An oral suspension was developed and used in Phase 3 clinical trials as part of the Bristol-Myers Squibb Company gatifloxacin paediatric New Drug Application. Additionally, a 50 mg paediatric tablet was also studied. Formulation details will be sought from the Bristol-Myers Squibb Company (Princeton, New Jersey, USA) for possible technology transfer. Scored 200mg and 400mg tablets could be developed easily.

6 International availability
Several generic products are on the market.

6.1 Patent status
The patent situation for gatifloxacin is publicly available in "Drugs in Focus January '10" (1), (details in Appendix 1). In addition WHO/TDR commissioned a search to Withers & Rogers in 2009.

Of the four patent families reported by the Key Patent Indicator (KPI), only the first family (claims to its chemical formula) is relevant to the use of gatifloxacin products for enteric fever. All expired in 2010 or earlier, except: (i) 2012 in Germany and Austria (through extension of patent) and (ii) 2011 in Germany, France and UK (data exclusivity expiry) but (a) extension in Australia and Germany were granted for brand name Tequin® which is discontinued and (b) no marketing authorization exists for gatifloxacin in Australia, France or UK. The latest patent to expire is in Canada although the product was voluntarily discontinued. There is no patent in the disease-endemic countries.

6.2 Production
Gatifloxacin is currently manufactured and sold by generic companies in India and China and freely available for export.

In India, the principal manufacturer of Approved Pharmaceutical Ingredient (API) is CIPLA Pharmaceuticals of Mumbai, who manufacture gatifloxacin sequihydrate as bulk material for export (2) and use by other companies in India (3).

CIPLA also manufacture gatifloxacin as tablets under the trade name Gatiquin as 200 and 400 mg tablets (4). There are at least 80 generic manufacturers currently supplying gatifloxacin formulated material in India. The individual presentations of generic gatifloxacin in India are in Appendix 2.

In China, there are a number of producers of API recorded, several of which produce to GMP standards, although the status of formulated gatifloxacin in the China market is more difficult to determine. Gatifloxacin is also available in Nepal, Vietnam, Pakistan and other countries in the region. Availability in other countries with endemic enteric fever is difficult to determine.

7 Listing is requested as an individual medicine
Individual medicine - gatifloxacin
Reasons are: resistance to first-generation fluoroquinolones; specific efficacy, safety data and supportive pharmacokinetic/pharmacodynamic and in vitro data; specific cost of product.
8 Information supporting the public health relevance

Enteric fever is widespread; conservative estimates have 26 million cases per year between *S. typhi* and *S. paratyphi*. Multidrug resistance (MDR = resistance to chloramphenicol, ampicillin and trimethoprim/sulfamethoxazole) and nalidixic acid resistance (NAR = reducing the sensitivity to the classical fluoroquinolones ofloxacin and ciprofloxacin) is widespread. Where MDR and NAR are common azithromycin and gatifloxacin are now the best options for treatment and can additionally treat other pathogens which may cause a clinical syndrome similar to enteric fever.

8.1 Epidemiology

Typhoid fever and paratyphoid fever are septicaemias caused by the Gram negative bacteria *Salmonella enterica* serovar Typhi (*S. typhi*) and *Salmonella enterica* serovar Paratyphi (*S. paratyphi*) A, B and C. Typhoid and paratyphoid fever are summarized as enteric fevers. Whilst *S. typhi* and *S. paratyphi* A and B infections are restricted to humans, *S. paratyphi* C can affect a variety of animals.

Enteric fever is endemic in Africa, Asia, Central and South America and found in parts of the Middle East, southern and eastern Europe (5). Improvement of infrastructure and sanitation has virtually eliminated typhoid fever in developed countries and infections seen in Europe, Australia, and North America are usually acquired abroad (mostly from the Indian Subcontinent, South East Asia and South America) (6). Current estimates from the World Health Organization (WHO) suggest that the global burden of typhoid fever is approximately 21 million cases annually with more than 210,000 deaths and that paratyphoid fever causes an additional 5 million cases (7). These numbers are based on extrapolating data from 22 studies that used blood culture, the gold standard for the diagnosis of typhoid fever. Many institutions in endemic countries lack blood culture facilities and the sensitivity of blood culture is less than 50% and so the true magnitude of the problem is undoubtedly greater. Transmission of typhoid fever occurs via the faeco-oral route by ingesting contaminated water or food or through direct contact. Chronic typhoid carriers involved in food handling are an important reservoir of infection. In endemic areas enteric fever is a disease of young school children through to young adults.

A WHO report has estimated the case fatality rate in enteric fever at 1% (7). The most important contributor to a poor outcome is a delay in appropriate antibiotic treatment made more likely by the presence of drug resistant strains in the community.

The geographical distribution of *S. typhi* and areas of multi-drug and nalidix acid resistance are in Figure 1.
8.2 Current treatment options and antibiotic resistance

8.2.1 Chloramphenicol

Chloramphenicol is a broad spectrum antibiotic with bacteriostatic activity. It was developed in 1947. Chloramphenicol and was the first antibiotic to be used in the treatment of typhoid fever (9).

Chloramphenicol treatment reduced typhoid fever mortality from 20% to approximately 1%, and the duration of fever from 2-4 weeks to 4-5 days (9-11). The most important adverse effect of chloramphenicol is a dose related, reversible bone marrow depression that results from inhibition of mitochondrial protein synthesis. This is relatively common and is reversible when the drug is stopped. In contrast, the chloramphenicol associated "idiosyncratic" aplastic anemia is very rare but is not dose related, non reversible and invariably fatal. Aplastic anemia is estimated to occur in 1 in 24,500 to 40,800 exposed (12). Resistance to chloramphenicol was first reported in the 1970s and has spread widely (13). Chloramphenicol remains of use for enteric fever in regions of the world where the bacteria are fully sensitive (5, 14, 15). However, disadvantages of chloramphenicol include the need for knowledge of the local sensitivity pattern, higher relapse and typhoid carrier rates (13) plus the need for treatment four times a day for 14-21 days (16) which reduces adherence.

8.2.2 Ampicillin and amoxicillin

The aminopenicillins ampicillin and amoxicillin have been evaluated for the treatment of typhoid fever in several clinical trials proved inferior to chloramphenicol (10, 13). Resistance is widespread and generally due to the production of the bacterial enzyme β-lactamase.
8.2.3 Trimethoprim-Sulfamethoxazole (cotrimoxazole)

Trimethoprim-sulfamethoxazole was widely used for the treatment of typhoid fever but with widespread resistance and an inferior efficacy it is rarely used today (13).

8.2.4 Extended spectrum cephalosporins

Cephalosporines exert bactericidal activity by interfering with the later stages of the bacterial cell wall synthesis (17). The target site of the β-lactam antibiotics including the cephalosporines are the penicillin-binding proteins (PBPs). Production of β-lactamases is the most common mechanism of bacterial resistance. In the late 90s, non-Typhi Salmonella producing extended spectrum β-lactamases (ESBL) have been reported in numerous countries. Resistance to extended spectrum cephalosporins has been reported in isolates of S. typhi from Bangladesh and Italy and S. paratyphi A from Pakistan and Nepal (18, 19). In 2009, a S. typhi isolate with ESBL phenotype caused by blaCTX-15 has been described in a patient returning from Iraq (20). The cephalosporines exhibit time dependent bactericidal activity.

Overall, the cephalosporines are a safe class of antibiotics, hypersensitivity reactions are the most common adverse events. Gastrointestinal reactions, including nausea, vomiting and diarrhoea are also reported frequently. The third generation cephalosporines ceftriaxone and cefixime have been used for the treatment of MDR typhoid fever. The fever clearance times in randomised trials using intravenous ceftriaxone have been 7-10 days and 10% of patients failed clinically. Relapse rates varied between 4% and 6% (5). A study in Pakistan evaluated either 7 or 14 days of ceftriaxone treatment in children with enteric fever and found a relapse rate of 14% (4 out of 28 patients) in the 7 day treatment group compared to no relapse in the 14 day group (21). The major disadvantage of ceftriaxone is the need for parenteral administration, the high cost, especially for what is often a prolonged treatment course.

Oral cefixime was a popular choice for the treatment of typhoid fever in children. In randomised controlled trials in children the mean Fever Clearance Times ranged from 5 to 8 days and clinical failure rates were reported to be below 3%.(22-24). However, a typhoid treatment trial in Vietnam reported much higher failure rates of 23% (10 out of 44 patients) when cefixime was used in children (25) and a recent trial in Nepal using Cefixime was stopped by the Independent Data and Safety Monitoring Committee because of an unacceptably high failure and relapse rate in those receiving cefixime. The overall treatment failure in this trial (acute treatment failure, relapsed patients plus one death) was determined to be (95% confidence interval) 37.6 % (27.14%–50.2%) in the cefixime group (26). Both S. typhi and S. paratyphi are predominantly intracellular organisms and the cephalosporines do not penetrate well intracellularly. This may explain the prolonged fever clearance times, higher relapse and carriage rates seen when these drugs are used.

8.2.5 Azithromycin

Azithromycin belongs to the macrolide class of antibiotics. Macrolides are inhibitors of protein synthesis by impairing the elongation of the peptidyl chain. Azithromycin resistance has not yet been reported in S. Typhi. Azithromycin has a bioavailability of 30% to 50%. The serum peak level is typically reached after 2 hours. Azithromycin has a large volume of distribution which is related to the ability to accumulate inside eukaryotic cells. The ratio of tissue to serum concentration for azithromycin is 50 to 1150 (27). The half life is 35 to 40 hours, which allows a single daily dose and shortened treatment regimen (3 to 5 days). Macrolides are primarily metabolised through cytochrome P450 and eliminated through the bile.
Gastrointestinal adverse events are frequent with macrolides. Macrolides have been associated with prolongation of the QT interval and should not be used in patients with concurrent administration of class IA and III antiarrhythmic agents and underlying cardiac disease. Azithromycin has become a treatment option for the treatment of MDR typhoid fever. The MICs for *S. typhi* to azithromycin range from 4 to 16 µg/ml (28). The peak serum level after a single dose of 500 mg of azithromycin is 0.4 mg/L (27). However, as azithromycin is concentrated more than 100 fold inside polymorphuclear cells and macrophages (29) and *S. typhi* is primarily an intracellular pathogen (30), effective drug concentrations are considerably above the MIC. In randomized clinical trials, azithromycin has been used for the treatment of MDR typhoid fever in children and adults in Egypt, India and Vietnam (31-35). Cure rates were good and outcomes in patients infected with nalidixic acid resistant *S. Typhi* were satisfactory (32).

### 8.2.6 Fluoroquinolones

Nalidixic acid, the prototype 4-quinolone antibiotic was discovered in 1962 (36), it is active against Gram negative bacteria and only achieves modest serum and tissue concentrations. Almost 20 years later, the addition of a fluorine molecule at position C6 created the fluoroquinolones. The 6-fluoro substituent confers a greater spectrum of activity against Gram negative and Gram positive pathogens, possibly by improving tissue penetration and binding to the DNA gyrase enzyme.

Ciprofloxacin and Ofloxacin (second generation fluoroquinolones) have excellent activity against Gram negative organisms (37). Due to its availability and affordability, ofloxacin has been widely used for the treatment of typhoid fever. However over the last few years strains resistant to nalidixic acid have appeared and spread widely. These strains are much less susceptible to both ciprofloxacin and ofloxacin with patients suffering from prolonged fever clearance times, clinical failures and prolonged carriage. Therefore the effectiveness of both of these drugs has declined leaving few options for treatment in regions with both multi-drug and nalidixic acid resistance.

Gatifloxacin is a broad spectrum 8-methoxy fluoroquinolone with enhanced activity against Gram positive organisms, which has received U.S. Food and Drug Administration (FDA) approval in 1999. It features a cyclopropyl group at position 1 similar to ciprofloxacin. The addition of a methoxy group at position 8 targets both topoisomerase II and IV and probably prevents (or delays) the development of quinolone resistance.

Fluoroquinolones are considered bactericidal agents and have excellent in vitro activity against a wide range of Gram negative and Gram positive organisms. The quinolones rapidly inhibit bacterial DNA synthesis, causing rapid cell death. The targets for the fluoroquinolones are the bacterial topoisomerase enzymes, DNA gyrase (topoisomerase II) and topoisomerase IV.

The main mechanism of quinolone resistance in *S. Typhi* is the accumulation of amino acid substitutions in the bacterial target enzyme DNA gyrase. The most commonly identified alteration has been a serine to phenylalanine substitution at position 83 of gyrA (38, 39). These mutations are focused around a region called the quinolone resistance determining region (QRDR). The QRDR of gyrA is close to tyrosine at position 122, the active site of the enzyme, which is covalently linked to DNA during strand breakage (40). Single point mutations in gyrA of *S. Typhi* leads to nalidixic acid resistance (MIC ≥ 32 µg/ml) and reduced susceptibility to the older generation fluoroquinolones. Single isolates of fully fluoroquinolone resistant *S. Typhi* and *S. Paratyphi A* have been reported from India (41). The high-level fluoroquinolone resistance seen in these *S. Typhi* (ciprofloxacin MIC ≥ 4 mg/ml) isolates was conferred by dual mutations in gyrA and a single mutation in parC (42, 43). Gatifloxacin binds with greater affinity to the QRDR and is less susceptible to these mutations remaining effective against these strains.
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The frequency of adverse reactions to quinolones is between 6 and 11% of the subjects exposed with less than 1% of adverse events being recorded as serious (44). The most frequent adverse effects reported are nausea, upper gastrointestinal discomfort and central nervous system effects such as headache, insomnia and dizziness. The adverse events are typically mild, self limited and mostly resolve when the drug is stopped. Some adverse effects do not seem to be related to specific modifications, whereas phototoxicity and CNS effects are linked to a specific structure. Each fluoroquinolone tends to produce a characteristic profile of adverse effects.

In their preclinical evaluation, all quinolones studied caused arthropathy in immature animals, especially in young beagle dogs and usually in the major weight bearing joints (45, 46). The concern that the fluoroquinolones might also cause cartilage damage in children has led to cautious use in many countries. However, extensive experience with the fluoroquinolones, especially ciprofloxacin and levofloxacin, in children suffering from cystic fibrosis, enteric fever and bacillary dysentery has provided a body of evidence suggesting that the joint damage seen in young dogs does not occur in children and these antibiotics are safe in children (5, 14, 47-49).

Fluoroquinolones have been associated with tendinitis and tendon rupture in adults, primarily affecting the Achilles tendon; risk factors were renal dysfunction and concomitant corticosteroid use (50). Severe neurotoxic reactions are rare. However, hallucinations, depression, and psychotic reaction have been reported. The quinolones should be used with caution in patients with known CNS disorders (e.g., epilepsy) or conditions predisposing to seizures (37, 44). The most common skin reactions are non-specific skin rashes, pruritus and urticaria. Phototoxicity is a rare dermatologic complication of quinolone therapy which is inextricably related to the chemical structure, a halogen grouping at position C8 (50).

A study based on post marketing surveillance data reported that the crude incidence rate (95% confidence interval) of cases of Torsades de Pointes (TdP) per 10 million prescriptions in the United States was 0.3 (0.0-1.1) for ciprofloxacin, 2.1 (0.3-7.6) for ofloxacin, 5.4 (2.9-9.3) for levofloxacin and 27 (12-53) for gatifloxacin (51). However questions regarding the validity of both the numerators and denominators used in these incidence calculations remain (52). Preclinical and clinical data indicate that levofloxacin, moxifloxacin, and gatifloxacin prolong the QTc interval. The potential for TdP to develop as a result of this is rare and is influenced by many independent variables, especially by concurrent administration of class IA and III antiarrhythmic agents, genetic susceptibility, underlying cardiac disease, electrolyte imbalance and organ impairment. Therefore gatifloxacin, levofloxacin, moxifloxacin or gemifloxacin should not be used in patients with risk factors predisposing them to TdP (52).

The quinolones as a class have demonstrated the ability to close K⁺-ATP channels in the β cells of the pancreas, resulting in the release of insulin and subsequent hypoglycaemia. However the mechanism for hyperglycaemia remains poorly understood and might be caused by overexposure (failure to adjust the dose in patients with renal failure) (52). Product labels for ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin mention the possibility of hypoglycaemia and hyperglycaemia. Although glucose disturbances appear to be a class effect, the odds of hypo- and hyperglycaemia appear to vary among the agents (53). A retrospective study in Texas reviewed records of dysglycaemia in hospitalised patients receiving gatifloxacin, levofloxacin, ciprofloxacin or ceftriaxone (54). Dysglycemic events were more likely to occur in patients receiving gatifloxacin (relative risk, 3.29; 95% CI, 2.33–4.65) or levofloxacin (relative risk, 1.55; 95% CI, 1.29–1.88) versus ceftriaxone.

In another study of elderly in-patients who received gatifloxacin or levofloxacin, gatifloxacin was independently associated with hypoglycaemia (OR, 2.4; 95% CI, 1.1–5.6) and hyperglycaemia (OR, 2.5; 95% CI, 1.6–3.9) versus levofloxacin (55). In diabetic patients treated with gatifloxacin, the overall incidence of hypoglycaemia was 0.4%, 0.7%, and 1.6%
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for patients below 65 years, 65 to 69 years and 80 years and above, respectively. The corresponding incidences of hyperglycaemia were 1.0%, 1.6%, and 3.3%, respectively (50).

When exposure to gatifloxacin was simulated in patients with severe hyperglycemia, who were often also older Type-2 diabetics with renal dysfunction, AUC values were 2 to 3 times those observed in patients with normal renal function (56). Therefore the authors suggested to empirically adjust the dose of gatifloxacin to 200 mg daily for patients aged above 65 years with community acquired respiratory tract infections. Only ciprofloxacin, clinafloxacin, enoxacin, grepafloxacin, pefloxacin, and tosufloxacin can inhibit the hepatic cytochrome \( \text{P}_450 \) isoenzyme CYP 1A4 isoenzymes. Few drugs are metabolized by these isoenzymes, but important drugs include the methylxanthines (theophylline and caffeine) and warfarin.

8.2.7 Summary of treatment options

In regions of the world where MDR and Nalidixic Acid strains of \( S. \text{typhi} \) and \( S. \text{paratyphi} \) are common azithromycin and gatifloxacin are now arguably the best options for treatment. Intravenous antibiotics are not appropriate in most settings where patients are treated as out-patients. In most parts of the world where enteric fever is common the sensitivity of the strains is not known as microbiological confirmation of the infection is lacking and formal testing of sensitivities is not undertaken. Hence most patients are treated empirically. In such circumstances a 7-day regimen of azithromycin or gatifloxacin are excellent choices for all strains of \( S. \text{typhi} \) and \( S. \text{paratyphi} \). The added value of these antibiotics is that they are effective against other pathogens which may cause a clinical syndrome similar to enteric fever. (see Section 9.2)

9 Treatment details

9.1 Dosage regimen and duration

The data presented in this application support the use of gatifloxacin at 10 mg/kg/d for 7 days (not to exceed 600 mg/day.)

This Section presents the pharmacological basis for this regimen. Efficacy results from randomised controlled studies are in Section 10.

We also present in this Section practical dosing schedules with existing formulations and prospective dosing with improved formulations.

9.2 Current clinical guidelines

There have been no formal WHO Guidelines published on the specific treatment for Enteric Fever. In 2003 the WHO Department of Vaccines and Biologicals produced an expert committee report “Background document: The diagnosis, treatment and prevention of typhoid fever” (14) in which the following recommendations were made:
Table 1. WHO recommendations from 2003 on optimal and alternative treatments for typhoid fever (NOTE: this table pre-dates the updated Cochrane Reviews and recent trials)

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>Antibiotic</th>
<th>OPTIMAL THERAPY</th>
<th>ALTERNATIVE EFFECTIVE DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily dose (mg/kg) Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chloramphenicol</td>
<td>50-75 14-21</td>
</tr>
<tr>
<td>Fully sensitive</td>
<td>Fluoroquinolone or ciprofloxacin</td>
<td>15</td>
<td>Amoxicillin</td>
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<tr>
<td></td>
<td></td>
<td>5-7</td>
<td>75-100 14</td>
</tr>
<tr>
<td></td>
<td>Multidrug resistance</td>
<td>15</td>
<td>15-20 7-14</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone or cefixime</td>
<td>15</td>
<td>Azithromycin</td>
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<td></td>
<td></td>
<td>15-20</td>
<td>15-20 7</td>
</tr>
<tr>
<td></td>
<td>Quinolone (nalidixic acid)</td>
<td>8-10</td>
<td>Cefixime</td>
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<tr>
<td></td>
<td>Azithromycin or ceftriaxone</td>
<td>7</td>
<td>20</td>
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<tr>
<td></td>
<td></td>
<td>75</td>
<td>7-14</td>
</tr>
</tbody>
</table>

a Three day courses are also effective and are particularly so in epidemic containment.
b The optimum treatment for quinolone resistant typhoid fever has not been determined.
Azithromycin, the third generation cephalosporines, or a 10-14 day course of high-dose fluoroquinolones is effective. Combinations of these are now being evaluated.

There have been a series of reviews since that date (5, 8, 57). The treatment options depend on local knowledge of the sensitivity patterns of the circulating strains of S. typhi and S. paratyphi (see Table 1). When culture facilities are not available and knowledge of the sensitivity patterns are unknown treatment decisions must be made empirically and consideration also given to the potential other causes and the differential diagnosis.

9.3 Summary target product profile

The ideal therapy would be an oral regimen; the drug would cure the patient quickly preferably as an outpatient, prevent the development of complications, and reduce the incidence of both short and long term carriage. The regimen would be easy to administer to enhance adherence, be effective against all strains of S. typhi and S. paratyphi, with no need for an antibiogram; it would have minimal adverse events and be affordable. As so much enteric fever is managed empirically it would be ideal if the therapy is also potentially effective against the common bacterial illnesses that can present like enteric fever.

Of all the treatments currently available the two drugs that fit this profile are gatifloxacin and azithromycin.

9.4 Pharmacological basis of gatifloxacin treatment regimen for enteric fever

Work presented in the Section provides evidence that

- the main determinant of gatifloxacin is the AUC\textsubscript{0-24}:MIC. A ratio >92.7 predicts favourable response in enteric fever.
- This ratio is achieved with a daily dose of 10mg/kg which produces consistent levels of exposure (little inter-individual variability) both in children and adults.
- Nalidix acid resistant organisms remain susceptible to gatifloxacin.
- Susceptibility screening and in vitro Salmonellae-specific breakpoints are not required for gatifloxacin.
9.4.1 Summary of antimicrobial drug resistance

In the late 1980s and early 1990s outbreaks of typhoid fever occurred that were resistant against all "first line" antimicrobials (multidrug resistance (MDR) defined as resistance to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) (5). These MDR S. Typhi isolates have been responsible for numerous outbreaks in countries in the Indian subcontinent, southeast Asia and Africa (8). All MDR strains so far examined have plasmids of the IncHI1 incompatibility group.

Consequently, the fluoroquinolones have become the treatment of choice for typhoid fever especially in areas of the world with MDR strains. The fluoroquinolones show excellent tissue penetration, accumulation in monocytes and macrophages and high drug levels in the gall bladder. However, there have been reports from Vietnam, India and Tajikistan of the emergence of S. Typhi isolates that respond less well to the fluoroquinolones (5, 8). In 1997, a typhoid epidemics in Tajikistan caused by such isolates caused more than 10000 illnesses and 108 deaths (58). Technically these isolates remain within the breakpoints set for fluoroquinolone susceptibility by the Clinical Laboratory Standard Institute (CLSI) (59), but they are resistant to nalidixic acid (the prototype quinolone) and show higher MICs to the fluoroquinolones. Patients infected with these isolates show a poor clinical response when treated with ciprofloxacin or ofloxacin. Of all the fluoroquinolones assessed, gatifloxacin showed the lowest minimum inhibitory concentrations (MICs) for nalidixic acid resistant S. typhi from Nepal (60) and Vietnam (38). In vitro time-kill experiments showed a reduction in the efficacy of ofloxacin against strains harbouring a single amino acid substitution at codon 83 or 87 of GyrA, this effect was more marked against a strain with a double substitution. The 8-methoxy fluoroquinolone gatifloxacin showed rapid killing of S. typhi harbouring both the single and double amino acid substitutions (38).

9.4.2 Pharmacodynamics and Pharmacokinetics of gatifloxacin in patients with enteric fever

Pre-clinical PK/PD models have long served as a basis for dose regimen selection in early drug development and, subsequently, PK/PD analyses of clinical data have served to confirm or refine pre-clinical PK/PD model predictions (61). The pre-clinical and clinical PK/PD of fluoroquinolone are better understood than perhaps any other class of antibacterial agents. The PK-PD relationship between exposure and response are understood in a wide range of indications, including community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute maxillary sinusitis, urinary tract infections, hospital-acquired pneumonia and typhoid fever (61).

Figure 2 presents the PK/PD indices that are used as surrogate markers for clinical and antimicrobial efficacy are the ratio of peak plasma concentration (C_{max}) of the antimicrobial to the minimum inhibitory concentration (MIC) of the pathogen (C_{max}/MIC), the ratio of the area under the concentration time curve 0 to 24 hours to the MIC (AUC>MIC) and the time above MIC (T>MIC). For the fluoroquinolones family in general antibacterial activity depends on the C_{max}/MIC and the AUC>MIC.
Abstract

Background. The pharmacodynamics of gatifloxacin in patients with typhoid fever and the positive- (predicts clinical cure) and negative- (predicts clinical failure) predictive value of the nalidixic acid screening test were evaluated in a randomized clinical trial.

Methods. Gatifloxacin-treated (10 mg/kg/day given orally for 7 days) patients with typhoid fever were analyzed. Previously validated population pharmacokinetic models were used in conjunction with patient-specific demographics to estimate individual patient drug exposures, as measured by the area under the concentration-time curve at 24 hours ($\text{AUC}_{0-24})$. Analyses included all patients with sufficient data to estimate $\text{AUC}_{0-24}$ and who had a defined minimum inhibitory concentration (MIC) value (N = 124). Fever was evaluated every 6 hours. Favourable clinical response was defined as the resolution of fever and symptoms within 48 hours of the end of therapy. Relapse was defined as the recurrence of fever and symptoms and/or the isolation of $S. \text{typhi}$ from blood after completion of therapy and discharge from hospital. A medical history, physical examination and stool cultures to determine chronic faecal carriage were performed at 1, 3 and 6 months after the end of therapy.

Findings. Statistically significant relationships between drug exposure intensity and clinical response were detected. In patients with a $\text{AUC}_{0-24}$:MIC ratios of greater than
92.7, 93.5% had a favourable response; while for those with $\text{AUC}_{0-24}/\text{MIC} \leq 92.7$, only 75% had a favourable response (odds ratio = 4.81, 95% CI 1.23, 18.9; $P = 0.02$). The positive- (predicts cure) and negative- (predicts failure) predictive value of the nalidixic acid screening test was 100.0% and 9.3%, respectively.

**Interpretation.** The exposure-response relationships identified provide a paradigm for dose regimen evaluation of existing and new fluoroquinolones for the treatment of typhoid fever. The results of this study also indicate that the nalidixic acid screening test was not predictive of clinical failure for gatifloxacin and *Salmonellae*-specific susceptibility breakpoints may be warranted.

**Population pharmacokinetics of gatifloxacin in south east Asian adult and paediatric patients with typhoid fever (see Appendix 4)**

**Background:** An understanding of patient pharmacokinetics (PK) is critical for the rational use of antibiotics. This is especially true for pathogens such as *Salmonella typhi* in South East Asian countries where the development of multi-drug resistance is an increasing concern. Gatifloxacin is a commonly used treatment in South East Asia for typhoid fever. We investigated gatifloxacin PK in paediatric patients and adult patients from Nepal with uncomplicated typhoid fever.

**Methods:** PK data were collected during routine clinical care. Each patient had ≤ 3 plasma samples for PK drawn after 3 - 6 days of oral gatifloxacin therapy. Separate candidate models for adults and children were fit to the data using Monte Carlo parametric expectation maximization with S-ADAPT. Due to the sparse nature of the PK sampling, the structure and covariate relationships from previous gatifloxacin adult and paediatric population PK models derived from infected North American patients were retained but were revised to fit the data from this population.

**Results:** 68 PK samples from 36 patients (aged 3 - 54 years) were analyzed. Gatifloxacin PK were best fit by a linear 1-compartment model. Fits of data were excellent ($r^2 > 0.9$ for children and adult data); interindividual variability in PK was modest. Compared to North American paediatric patients, the Nepalese paediatric patient population had ~50% slower clearance (Table 2).

**Conclusions:** As drug clearance was markedly lower in South East Asian typhoid fever vs infected North American patients, these data demonstrate the importance of evaluating PK in varying patient populations. The PK models described herein will be used in future pharmacokinetics-pharmacodynamics (PK-PD) analyses of efficacy in South East Asian populations with typhoid fever.

**Table 2. Main parameters of gatifloxacin derived from population kinetics of Asian enteric fever patients**

<table>
<thead>
<tr>
<th>Patient population</th>
<th>PK parameter</th>
<th>Previous models</th>
<th>Current data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric</strong></td>
<td>CL/F (L/h/m²)</td>
<td>8.46 (3.50)</td>
<td>4.41 (5.65)</td>
</tr>
<tr>
<td></td>
<td>Vc (L/kg)</td>
<td>2.15 (3.30)</td>
<td>1.21 (13.8)</td>
</tr>
<tr>
<td><strong>Adult</strong></td>
<td>CL/F, nonrenal (L/h)</td>
<td>8.11 (35.3)</td>
<td>2.91 (21.9)</td>
</tr>
<tr>
<td></td>
<td>CL/F, renal-slope* (L/h/mL/min)</td>
<td>0.0629 (37.8)</td>
<td>0.0629 (---)</td>
</tr>
<tr>
<td></td>
<td>Vc (L/kg)</td>
<td>1.45 (7.9)</td>
<td>1.28 (17.7)</td>
</tr>
</tbody>
</table>

*This parameter was not fit due to the narrow range of renal function
## 9.5 Proposed dosing regimens

Gatifloxacin is currently formulated as 200mg and 400mg strength non scored tablets. Tablet fractionation is custom both in clinical practice and clinical trials.

We present here proposed practical dosing regimens using the current formulations and prospected improved formulations. The target dose was set at 10mg/kg and the therapeutic window at 7-13.5mg/kg/d not to exceed 600mg/d. This range is consistent with how gatifloxacin was originally developed by Bristol-Meyers Squibb and with the pharmacokinetic/pharmacodynamic data and safety margins in children and adults.

The objective was to administer whole tablets and minimize tablet crushing.

We also wanted to predict what proportion of the typical enteric fever patient population will be receiving which dose. The proportions of the overall population in the tables below refer to the weight frequencies found in the Nepal plus Vietnam database of 1208 enteric fever patients (weight distribution in Figure 3 below.)

**Figure 3. Weight distribution of Asian enteric fever patients**

Option 1 uses the current non scored 200mg and 400mg tablets. It was not possible to give whole tablets for patients under 15kg body weight (*) for whom tablet crushing remains the only option. Patients weighing 29kg taking one 200mg tablet will be receiving 6.9mg/kg instead of the 7mg/kg. Because of the 600mg maximum dose patients weighing =>87kg will received <7mg/kg.
Table 3. Practical dosing of gatifloxacin with current non scored 200mg and 400mg tablets

<table>
<thead>
<tr>
<th>Weight band</th>
<th>% Population</th>
<th>mg/kg/d</th>
<th>mean</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15*</td>
<td>9.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 to 29</td>
<td>34.2%</td>
<td>200</td>
<td>9.5</td>
<td>6.9</td>
<td>13.3</td>
</tr>
<tr>
<td>30 to 49</td>
<td>29.6%</td>
<td>400</td>
<td>10.4</td>
<td>8.2</td>
<td>13.3</td>
</tr>
<tr>
<td>&gt;= 50</td>
<td>26.5%</td>
<td>600</td>
<td>8.8</td>
<td>6.7</td>
<td>12.0</td>
</tr>
</tbody>
</table>

Option 2 refers to the possibility that manufacturers will accept to develop 200mg and 400mg tablets scored in half (or 400mg tablets scored to give four 100mg units). (* ) patients weighing less than 15kg the dosing range displayed is for the weight range 8.5kg to <15kg, below which tablet crushing is required to avoid overdosing. Because of the 600mg maximum dose, patients weighing =>87kg will received <7mg/kg.

Table 4. Practical dosing of gatifloxacin with scored 200mg and 400mg tablets

<table>
<thead>
<tr>
<th>Weight band</th>
<th>% Population</th>
<th>mg/kg/d</th>
<th>mean</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15kg*</td>
<td>9.8%</td>
<td>100</td>
<td>9.4</td>
<td>7.1</td>
<td>12.5</td>
</tr>
<tr>
<td>15 to 24</td>
<td>27.1%</td>
<td>200</td>
<td>10.5</td>
<td>8.3</td>
<td>13.3</td>
</tr>
<tr>
<td>25 to 34</td>
<td>12.0%</td>
<td>300</td>
<td>10.3</td>
<td>8.8</td>
<td>12.0</td>
</tr>
<tr>
<td>35 to 49</td>
<td>24.6%</td>
<td>400</td>
<td>9.6</td>
<td>8.2</td>
<td>11.4</td>
</tr>
<tr>
<td>&gt;= 50</td>
<td>26.5%</td>
<td>600</td>
<td>8.8</td>
<td>6.7</td>
<td>12.0</td>
</tr>
</tbody>
</table>

10 Summary of comparative effectiveness

10.1 Identification of clinical evidence

The current Cochrane review (57) is being updated. We completed a comprehensive search in October 2010 and have screened this and retrieved full text articles. The inclusion criteria remain the same as the current published Cochrane review.

In the updating of this review, we will use the Cochrane new risk of bias assessment. We will use GRADE to summarize the results. This will be using relative risk with confidence intervals across meta-analysis of comparisons for standard outcomes where this is appropriate. (the updated review will be submitted at a later stage as Appendix 5.)

10.2 Recent randomised comparative clinical trials

Recent clinical trials compared gatifloxacin to:

Azithromycin:
Background: Drug resistant typhoid fever is a major clinical problem globally. Many of the first line antibiotics, including the older generation fluoroquinolones, ciprofloxacin and ofloxacin, are failing.

Objectives: We performed a randomised controlled trial to compare the efficacy and safety of gatifloxacin (10 mg/kg/day) versus azithromycin (20 mg/kg/day) as a once daily oral dose for 7 days for the treatment of uncomplicated typhoid fever in children (above 6 months) and adults in Vietnam.

Methods: An open-label multi-centre randomised trial with pre-specified per protocol analysis and intention to treat analysis was conducted. The primary outcome was fever clearance time, the secondary outcome was overall treatment failure (clinical or microbiological failure, development of typhoid fever-related complications, relapse or faecal carriage of S. typhi). Patients were followed up at 1, 3 and 6 months.

Principal findings: We enrolled 358 children and adults with suspected typhoid fever, 186 patients were treated with gatifloxacin and 172 with azithromycin. There was no death in the study. 287 patients had blood culture confirmed typhoid fever, 145 patients received gatifloxacin and 142 patients received azithromycin. The median FCT was 106 hours in both treatment arms (95% Confidence Interval [CI]; 94-118 hours for gatifloxacin versus 88-112 hours for azithromycin), (logrank test \( p = 0.984 \), HR [95% CI] = 1.0 [0.80-1.26]).

Overall treatment failure occurred in 13/145 (9%) patients in the gatifloxacin group and 13/140 (9.3%) patients in the azithromycin group, (logrank test \( p = 0.854 \), HR [95% CI] = 0.93 [0.43–2.0]). 96% (254/263) of the Salmonella enterica serovar Typhi isolates were resistant to nalidixic acid and 58% (153/263) were multidrug resistant.

Conclusions: Both antibiotics showed an excellent efficacy and safety profile. Both gatifloxacin and azithromycin can be recommended for the treatment of typhoid fever particularly in regions with high rates of multidrug and nalidixic acid resistance. The cost of a 7-day treatment course of gatifloxacin is approximately one third of the cost of azithromycin in Vietnam.

Trial registration: Current Controlled Trials ISRCTN 67946944

Cefixime:
This trial was stopped early by the independent Data Safety and Monitoring Board due to the inferior performance of cefixime. An open randomized comparison of gatifloxacin versus cefixime for the treatment of uncomplicated enteric fever.


Objective. To assess the efficacy of gatifloxacin versus cefixime in the treatment of uncomplicated enteric fever.

Design. A randomized, open-label, active control trial with two parallel arms. Setting. Emergency Room and Outpatient Clinics in Patan Hospital, Lalitpur, Nepal.

Participants. Patients (aged two to sixty-five years) with clinically diagnosed uncomplicated enteric fever meeting the inclusion criteria. Interventions. Patients were allocated to receive one of two drugs, Gatifloxacin or Cefixime. The dosages used were Gatifloxacin 10 mg/kg, given once daily for 7 days, or Cefixime 20 mg/kg/day given in two divided doses for 7 days.

Outcome Measures. The primary outcome measure was fever clearance time. The secondary outcome measure was overall treatment failure (acute treatment failure and relapse). Patients were followed up for 6 months.

Results. Randomization was carried out in 390 patients before enrollment was suspended on the advice of the independent data safety monitoring board due to
Gatifloxacin for enteric fever

significant differences in both primary and secondary outcome measures in the two arms and the attainment of a priori defined endpoints. Among all randomized patients, 187 patients were assigned to receive cefixime and 203 to gatifloxacin. 77 patients assigned to receive cefixime were blood culture positive for enteric fever whilst 92 of those assigned to receive gatifloxacin were culture positive.

Median (95% confidence interval) fever clearance times were 92 hours (84–114 hours) for gatifloxacin recipients and 138 hours (105–164 hours) for cefixime-treated patients (Hazard Ratio[95%CI] = 2.171 [1.545–3.051], p<0.0001). 19 out of 70 (27%) patients who completed the 7 day trial had acute clinical failure in the cefixime group as compared to 1 out of 88 patients (1%) in gatifloxacin group (Odds Ratio [95%CI] = 0.031 [0.004 – 0.237], p<0.001). Overall treatment failure patients (relapsed patients plus acute treatment failure patients plus death) numbered 29. They were determined to be (95% confidence interval) 37.6% (27.14–50.2%) in the cefixime group and 3.5% (2.2–11.5%) in the gatifloxacin group (HR[95%CI] = 0.084 [0.025–0.280], p<0.0001). There was one death in the cefixime group. This trial was stopped early by the independent Data Safety and Monitoring Board due to the inferior performance of cefixime.

Conclusions. Based on this study, gatifloxacin is a better treatment for uncomplicated enteric fever than cefixime.

Trial Registration. Current Controlled Trials ISRCTN75784880

Chloramphenicol (Appendix 4):
A randomised controlled trial of gatifloxacin versus chloramphenicol for the treatment of uncomplicated enteric fever in Nepalese children and adults:

Background: It is unclear whether chloramphenicol is a reliable therapy for enteric fever or whether gatifloxacin, a newer generation and affordable fluoroquinolone, would be the better choice.

Objectives: To determine the efficacy of chloramphenicol versus gatifloxacin in the treatment of uncomplicated enteric fever.

Participants: Patients (aged two to sixty-five years) from Patan Hospital, Kathmandu, Nepal with clinically diagnosed with enteric fever who met the inclusion criteria.

Intervention: Patients received either gatifloxacin (10 mg/kg) once a day for 7 days or chloramphenicol (75 mg/kg/day) in four divided doses for 14 days.

Outcome measures: The primary outcome measure was treatment failure which comprised of persistent fever at day 10, need for rescue treatment, microbiological failure, relapse until day 31, and enteric fever related complications. The secondary outcome measure was fever clearance time, late relapse, and faecal carriage. Patients were followed up for 6 months.

Results: One thousand one hundred and fifty one patients were assessed for eligibility of which 853 were randomized and 844 were analyzed. Of these 418 were in the chloramphenicol arm and 426 were in the gatifloxacin arm. Out of the 844 patients, 352 patients had blood culture confirmed enteric fever, 175 in the chloramphenicol arm and 177 in the gatifloxacin arm. There were 14 treatment failure patients in the chloramphenicol arm and 12 in the gatifloxacin arm (Hazard Ratio [95% CI]= 0.86 [0.40 to 1.86], p=0.70). Major side effects for chloramphenicol (bone marrow suppression) or gatifloxacin (dysglycemia) were not encountered although, nausea, dizziness, and diarrhea were worse in the chloramphenicol group. Only 0.5% (2/352) of the isolates were multidrug resistant (MDR), but 71% (251/352) were nalidixic acid resistant.

Conclusion: This large clinical trial of culture confirmed enteric fever showed that both chloramphenicol and gatifloxacin had an excellent efficacy in this young population, in
Gatifloxacin for enteric fever

a region with full sensitivity to chloramphenicol and over 70% resistance to nalidixic acid. Treatment duration, ease of administration, decreased side effects and expense favours the usage of gatifloxacin.

Trial Registration. Current Controlled Trials ISRCTN 53258327. Funding: Wellcome Trust.

Ofloxacin:
An open randomised comparison of gatifloxacin versus ofloxacin for the treatment of uncomplicated enteric fever; ISRCTN63006567). This is an on-going trial. As of November 2010 approximately 500 patients have been enrolled.

10.3 Meta-analysis of the above RCTs of gatifloxacin for enteric fever

Two of the above RCTs (gatifloxacin vs. azithromycin and vs. cefixime) were already included in the previous Cochrane systematic review. A third study (vs. chloramphenicol) is being submitted for publication and will be included in the updated systematic review. These studies total 414 gatifloxacin and 394 active control patients.

This preliminary meta-analysis is based on overall failures (primary failure and relapse). No difference is found between gatifloxacin and azithromycin and between gatifloxacin and chloramphenicol; gatifloxacin is significantly more effective than cefixime. The latter comparison explains the heterogeneity found on aggregate (I-square = 87%).
11 Summary of comparative evidence on safety

- The class and product-specific safety liabilities are known.
- The safety profile presented here is derived from RCTs of enteric fever and pulmonary tuberculosis.
- There is no evidence from studies at the target dose in the target population that patients on gatifloxacin will be at a particular risk of dysglycaemia. This is further confirmed by data from tuberculosis patients exposed to ~25 times the total dose used for enteric fever.
- The drug is well-tolerated in patients with enteric fever; the gatifloxacin safety profile is similar to that of the comparator drugs.

11.1 Class and product-specific safety liabilities

Gatifloxacin is a fourth-generation fluoroquinolone antibiotic that, like other members of that family, inhibits the bacterial enzymes DNA gyrase and topoisomerase IV. Gatifloxacin is generally well tolerated. In common with all broad-spectrum antibiotics, gastrointestinal disturbances may be encountered. The fluoroquinolones are also known to have a number of adverse effects that are considered to be common to the class, although the severity of these varies considerably between compounds. These include effects on cardiac conduction, collagen formation (e.g. tendon rupture), photosensitivity, and dysglycaemia. While another 4th generation fluoroquinolone, moxifloxacin, has significant effects on cardiac repolarisation (prolongation of QT interval), this appears to be absent with gatifloxacin. In contrast, dysglycaemic effects (hypoglycaemia at the beginning of treatment, followed later by hyperglycaemia) are most commonly reported with gatifloxacin. (see also Section 8.2.6)

Hints of gatifloxacin-associated effects on glucose homeostasis were first noted during preclinical development. Preclinical studies which administered up to 19 times the 400 mg dose for up to 6 months demonstrated a dose related decrease in insulin release in pancreatic β-cells in all species studied (62). Shortly after gatifloxacin was introduced, case reports of effects on glucose homeostasis began to emerge. Patients identified as "at risk" included those with non-insulin-dependent diabetes on therapy and elderly patients with age-related decreases in renal function (56).

In summary, these data demonstrate
- a mechanism of gatifloxacin-associated dysglycemia that is
dose- (exposure) dependent,
- patients especially at risk include non-insulin-dependent diabetics treated with oral hypoglycemic medications, and
- elderly patients with age-related changes in renal function.

Gatifloxacin-associated dysglycaemia was not noted during the course of the paediatric development programme and a large trial in children with otitis media followed for one year demonstrated no dysglycaemia adverse effects (63). The concerns of dysglycaemia in elderly Canadian patients were further heightened with the retrospective report in 2006 in the NEJM, concerning older, severely ill in-patients with a history of diabetes (64). That study received worldwide publicity leading to the drug being withdrawn in many countries.

Subsequent work (far less publicized) questioned whether these effects were any more severe or common compared to other fluoroquinolones and comparable antibiotics in an outpatient setting (65). In addition, patients with enteric fever are typically children and young adults and thus are very rarely non-insulin-dependent diabetics and have good kidney function. Clearly in these two very different populations gatifloxacin’s dysglycaemia adverse effect profile is very different.
Between Nepal and Vietnam in recent years in registered clinical trials almost 1500 young patients suffering from enteric fever, shigellosis and TB meningitis were treated with gatifloxacin with no problems noted in glucose control. Of these, over 600 patients were followed up for six months and no episodes of dysglycaemia have been seen (26, 66) and ISRCTN53258327 (An open randomised study to assess the efficacy of gatifloxacin versus chloramphenicol for the treatment of uncomplicated typhoid fever in Kathmandu, Nepal; manuscript submitted as appendix) and ISRCTN63006567 (An open randomised comparison of gatifloxacin versus ofloxacin for the treatment of uncomplicated enteric fever; ongoing). In addition, dysglycaemia has not emerged as a side effect attributable to gatifloxacin in 917 patients receiving gatifloxacin daily for four months as part of a drug combination regimen for the treatment of pulmonary tuberculosis in a multicentre RCT in Africa (Senegal, Benin, Guinea, Kenya and South Africa). Blood glucose analysis from the above studies is presented below.

As compared to the elderly Canadian patients, the profile of the enteric fever patients as derived from 1211 patients with age recorded enrolled in two RCTs in Nepal and Vietnam is that of a younger population (overall: median age 13 year, interquartile range 8-21 years; median weight 36kg, interquartile range 19.5-50kg).

Table 5. Age(n=853) and weight(n=850) profile of enteric fever patients from two RCTs in Nepal and Vietnam.

<table>
<thead>
<tr>
<th>Nepal Age</th>
<th>Nepal Weight</th>
<th>Vietnam Age</th>
<th>Vietnam Weight</th>
<th>Combined Age</th>
<th>Combined Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>count</td>
<td>853</td>
<td>850</td>
<td>358</td>
<td>358</td>
<td>1211</td>
</tr>
<tr>
<td>median</td>
<td>16</td>
<td>42</td>
<td>11</td>
<td>23.3</td>
<td>13</td>
</tr>
<tr>
<td>Q25</td>
<td>9</td>
<td>21</td>
<td>7</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Q75</td>
<td>22</td>
<td>52</td>
<td>15</td>
<td>40</td>
<td>21</td>
</tr>
</tbody>
</table>

11.2 Analysis of blood glucose in RCTs of enteric fever and pulmonary tuberculosis

We present here an analysis of blood glucose as dysglycaemia has been identified as a particular safety liability for this compound (see above.) We have detailed data from randomised controlled trials (RTCs) on enteric fever (~10mg/kg/d x 7d, n=422 gatifloxacin-treated patients) and tuberculosis (400mg/d 6 days a week in combination with rifampicin,
Gatifloxacin for enteric fever

isoniazid and pyrazinamide for initial 2 months and in combination with rifampicin and isoniazid for the following 2 months, n=917 gatifloxacin-treated patients).

11.2.1 Blood glucose levels in enteric fever

Blood glucose levels were monitored during the trial of gatifloxacin versus chloramphenicol in Nepalese children (above 2 years) and adults (ISRCTN53258327). Random blood glucose (RBG) was measured daily on days 1 to 8, on day 15 and at one month. On days 2 to 7, during the evening visit, the blood glucose was measured by finger-prick testing (OneTouch SureStep™, Johnson & Johnson, USA) by the Community Medical Assistants. HbA1c was measured at 3 months.

For the analysis and grading of adverse events including blood glucose, the NIH Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (“DAIDS AE grading table”) was used.

Table 6. Parameters used in the analysis of severity of disglycaemia

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MILD</td>
<td>MODERATE</td>
<td>SEVERE</td>
<td>POTENTIALLY LIFE-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>THREATENING</td>
</tr>
<tr>
<td>Nonfasting Glucose, serum, high</td>
<td>116 – 160 mg/dL</td>
<td>161 – 250 mg/dL</td>
<td>251– 500 mg/dL</td>
<td>&gt; 500 mg/dL</td>
</tr>
<tr>
<td>HYPERGLYCEMIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfasting Glucose, serum, low</td>
<td>55 – 64 mg/dL</td>
<td>40 – 54 mg/dL</td>
<td>30 – 39 mg/dL</td>
<td>&lt; 30 mg/dL</td>
</tr>
<tr>
<td>HYPOGLYCEMIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following information regarding RBG and HbA1c was summarized:

- Median (IQR) levels for each visit (e.g. daily until day 8, day 15, and month 1 for random glucose and at day 90 for HbA1c)
- Worst hyperglycemia grade overall, during days 1-8, at day 15, or at month 1 (contingency tables of frequencies by treatment arm)
- Worst hypoglycemia grade overall, during days 1-8, at day 15, or at month 1 (contingency tables of frequencies by treatment arm)
- Median (IQR) levels of HbA1c at month 3.
- Proportion of patients with HbA1c >6% at month 3.

Table 7 shows the numbers of hyper- and hypoglycaemias in both treatment arms and Table 8 shows the median random glucose levels. There were more non-fasting grade 2 hyperglycaemias (160-250 mg/dl) in patients in the gatifloxacin group with 42/414 (10.14%) compared to 25/407 (6.14%) in the chloramphenicol group (p=0.04) during treatment (day 2 to day 7). There were no non-fasting hyperglycaemia events noted on day 15. The proportion of patients with an elevated glycosylated Haemoglobin (HbA1C) level between 6 and 7.5% at 3 months was similar in the two groups.

Median glucose levels (Table 8) tended to be higher on days 2 to 7 during treatment in both arms. Median glucose levels on days 4 to 8 were slightly, but significantly, higher in the gatifloxacin arm compared to the chloramphenicol arm.
**Table 7 Disglycaemia. Patients with abnormal non-fasting blood glucose. Numbers with (% of those tested)**

<table>
<thead>
<tr>
<th></th>
<th>Chloramphenicol</th>
<th>Gatifloxacin</th>
<th>Comparison (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperglycemia, Grade 2</strong>#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Baseline</td>
<td>1/414 (0.24)</td>
<td>2/422 (0.47)</td>
<td>-</td>
</tr>
<tr>
<td>On Day2 to Day7*</td>
<td>25/407 (6.14)</td>
<td>42/414 (10.14)</td>
<td>0.04</td>
</tr>
<tr>
<td>On Day8</td>
<td>0/402 (0)</td>
<td>1/400 (0.25)</td>
<td>0.5</td>
</tr>
<tr>
<td>On Day15</td>
<td>1/366 (0.27)</td>
<td>0/351 (0)</td>
<td>1</td>
</tr>
<tr>
<td>On Month1</td>
<td>1/375 (0.27)</td>
<td>0/383 (0)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Hypoglycemia, Grade2@ or worse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Baseline</td>
<td>4/414 (0.97)</td>
<td>4/426 (0.95)</td>
<td>-</td>
</tr>
<tr>
<td>On Day2 to Day7*</td>
<td>1/407 (0.25)</td>
<td>1/414 (0.24)</td>
<td>1</td>
</tr>
<tr>
<td>On Day8</td>
<td>2/402 (0.50)</td>
<td>2/400 (0.50)</td>
<td>1.00</td>
</tr>
<tr>
<td>On Day15</td>
<td>3/366 (0.82)</td>
<td>3/351 (0.85)</td>
<td>1.00</td>
</tr>
<tr>
<td>On Month1</td>
<td>3/375 (0.80)</td>
<td>4/383 (1.04)</td>
<td>1</td>
</tr>
<tr>
<td><strong>HbA1c &gt;6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On Month3</td>
<td>22 (6.27)</td>
<td>20 (5.57)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* On Days 2 to 7 all patients were monitored with fingerstick glucose testing.
# Hyperglycemia grade 2 defined as non-fasting plasma glucose level between 161 and 250 mg/dL. No grade 3 hyperglycaemias were observed.
@Hypoglycaemia grade 2 defined as non-fasting plasma glucose between 40 and 54 mg/dL

**Table 8 Median daily random blood glucose level in enteric fever patients treated with chloramphenicol or gatifloxacin. Median glucose levels in mg/dl. n = Number of patients. Comparisons based on Wilcoxon test.**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Chloramphenicol</th>
<th>Gatifloxacin</th>
<th>Comparison (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Glucose mg/dl</td>
<td>Glucose mg/dl</td>
<td>Glucose mg/dl</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td>836</td>
<td>87 77-98</td>
<td>414</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td>805</td>
<td>105 92-119</td>
<td>396</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td>784</td>
<td>106 94-119</td>
<td>389</td>
</tr>
<tr>
<td>Day 4</td>
<td></td>
<td>776</td>
<td>108 97-121.25</td>
<td>383</td>
</tr>
<tr>
<td>Day 5</td>
<td></td>
<td>767</td>
<td>107 96-121</td>
<td>383</td>
</tr>
<tr>
<td>Day 6</td>
<td></td>
<td>769</td>
<td>105 96-119</td>
<td>380</td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td>754</td>
<td>106 96-117</td>
<td>379</td>
</tr>
<tr>
<td>Day 8</td>
<td></td>
<td>802</td>
<td>84 74-95</td>
<td>402</td>
</tr>
<tr>
<td>Day 15</td>
<td></td>
<td>717</td>
<td>81 73-91</td>
<td>366</td>
</tr>
<tr>
<td>Day 30</td>
<td></td>
<td>758</td>
<td>83 74-93</td>
<td>375</td>
</tr>
</tbody>
</table>

**11.2.2 Blood glucose levels in pulmonary tuberculosis (Appendix 7)**

**Context**
The data analysed are from a randomised open-label controlled trial of a 4 month gatifloxacin-containing regimen versus standard 6 month regimen for the treatment of adult patients with pulmonary tuberculosis. This trial has been conducted in 5 countries in Africa (Benin, Guinea, Kenya, Senegal and South Africa). The recruitment started in January 2005 and the study will end in April 2011.
Gatifloxacin for enteric fever

Method
Male or female patients, aged 18 to 65 years, currently suffering from recently diagnosed microscopically proven pulmonary tuberculosis and providing informed consent were eligible for inclusion in the study. In the Gatifloxacin arm, patients took Gatifloxacin at the dose of 400mg daily (6 days per week), irrespective of weight, for 4 months; in association with Rifampicin, Isoniazid and Pyrazinamide during the first 2 months of TB treatment and Rifampicin, Isoniazid for the last 2 months.

Initially blood glucose measurements were taken at baseline (pre-randomisation; visit 1), week 4 (visit 3), 8 (visit 4) and end of treatment visits (either visit 6 or 8 depending on treatment arm), by finger-prick or full blood tests. During the study recruitment period additional sampling times were incorporated based on the recommendation from the Data Monitoring Committee. These were: 4 hours following first treatment dose, day 7, 14 and week 12 (visit 5) from randomisation. The measurement taken 4 hours after first dose was not taken when fasting as patients were allowed to eat 30 minutes after first drug intake.

This report provides a summary, by treatment arm, of the (i) frequency of hypoglycaemic (less than or equal to 3.5 mmol/L), normal (3.51-6.39 mmol/L) and hyperglycaemic (greater than or equal to 6.4 mmol/L) events, (ii) severity of these events, and (iii) incidence rates of hyperglycaemic events.

Results and conclusion
A total of 1,836 patients have been recruited in this trial of whom 917 were randomised to the Gatifloxacin arm. In the Gatifloxacin arm the approximate mean age and weight were 30 years and 55kg, respectively. Based on the data analysed, the incidence rates of dysglycaemic events were similar in the Gatifloxacin and control arms.

11.3 Summary of comparative safety against comparators in RCTs of enteric fever

In randomized controlled trials comparing gatifloxacin to azithromycin (66), cefixime (26) and chloramphenicol; gatifloxacin was extremely well tolerated.

Gatifloxacin versus azithromycin
Both treatments were well tolerated. One adverse event related to azithromycin was reported, a maculopapular rash that occurred after the first dose of treatment. Azithromycin was discontinued immediately and the patient was treated with ceftriaxone. Gastrointestinal side-effects (change in consistency and frequency of stools) that were probably typhoid fever related were relatively frequent in both treatment arms at the start of treatment. In the gatifloxacin group, one patient experienced vomiting on day 2 and day 3 and one patient had diarrhoea (4 episodes/ day) on day 4 and day 5 of treatment. These episodes were self-limiting and did not require the interruption of therapy.

The median levels of serum AST and ALT fell in both groups after 7 days of therapy. In the culture positive group, the median post-treatment AST was 46.35 U/L (range 12.8 – 217.5) in the gatifloxacin arm and 45 U/L (range 5 – 358) in the azithromycin arm.

Gatifloxacin versus cefixime
There was one death in the cefixime group. This might have been due to the development of disease-related complications during treatment. The 16 year old patient was enrolled on the fourteenth day of his illness. On day 6 of treatment the patient complained of reddish stool and petechiae and was immediately admitted to hospital where he developed severe thrombocytopenia and gastrointestinal bleeding. He developed acute respiratory distress syndrome and was mechanically ventilated. He developed disseminated intravascular coagulation and succumbed to his illness on day 21 of entry into the trial. His pretreatment
blood culture grew S. Paratyphi A which was sensitive to cefixime with an MIC of 0.38 mg/mL. One patient developed erythematous skin rash which needed two doses of oral antihistamine.

Among all patients who received gatifloxacin there were 2 patients with excessive vomiting, which required intravenous anti-emetics and fluids and observation in the hospital emergency room for up to 6 hours. There was an additional 23 patients who complained of excessive nausea and occasional vomiting after ingestion of the drug. Of these, two needed oral antiemetics; in the remaining 21 patients no intervention was required.

**Gatifloxacin versus chloramphenicol**

A comparison of adverse events in the two randomized arms is shown in Table 9. Adverse events were mild (grades 1 and 2). Anorexia, diarrhoea, nausea and dizziness were significantly more common in the chloramphenicol arm of the study. Three patients in the chloramphenicol arm who had a white cell count between 1500-1999/mm² on day 5 to 8 and had their chloramphenicol stopped. The fever had already defervesced when the drug was stopped and they did not relapse for 6 months. There were no life-threatening complications of enteric fever in this study.

Table 9. Adverse events in enteric fever patients treated with chloramphenicol or gatifloxacin.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Chloramphenicol (n=418)</th>
<th>Gatifloxacin (n=426)</th>
<th>Comparison (p value)#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients with event (%)</td>
<td>Number of Events</td>
<td>Number of Patients with event (%)</td>
</tr>
<tr>
<td>Any selected AE</td>
<td>99 (23.68%)</td>
<td>168</td>
<td>59 (13.85%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (2.63%)</td>
<td>12</td>
<td>8 (1.88%)</td>
</tr>
<tr>
<td>Acne</td>
<td>2 (0.48%)</td>
<td>2</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (2.15%)</td>
<td>10</td>
<td>1 (0.23%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>24 (5.74%)</td>
<td>26</td>
<td>5 (1.17%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (2.63%)</td>
<td>11</td>
<td>2 (0.47%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (6.22%)</td>
<td>29</td>
<td>9 (2.11%)</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>4 (0.96%)</td>
<td>4</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36 (8.61%)</td>
<td>39</td>
<td>35 (8.22%)</td>
</tr>
<tr>
<td>Weakness</td>
<td>4 (0.96%)</td>
<td>4</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Note: All adverse events in this list were non-severe, ie Grade I or Grade II

# Fisher’s exact test comparing the number of patients with an event.

12 Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

A variety of generic products is on the market, all generally cheap. We retrieved information and compared costs with alternative treatment options. We also used enteric fever patient data to produce specific estimates of cost of drug when enteric fever is treated with gatifloxacin. Other direct costs and indirect costs could not be quantified for the moment. The cost of illness of enteric fever is poorly characterised.
This section shows that:

- Gatifloxacin is the cheapest of all treatments of enteric fever. Azithromycin (the only alternative that could be used in areas of MRD and NAR) is 2-5 times as expensive.
- Treating 1000 patients with the current products (200 and 400mg tablets) will cost 4150$. 

12.1 Economic burden of enteric fever

There have been very few studies of the economic burden of illness in regions where enteric fever is endemic. In 2004 from India the estimated direct and indirect costs to the family of an episode of enteric fever ranged between 150US$ - 550US$, depending on whether the patient was treated as an out-patient or required admission to hospital (67). Neither of these estimates included the costs incurred during relapses or the costs associated with patients who develop long term carriage and pass on the infection to others in their community.

12.2 Direct costs: comparison of drug costs for treatment of enteric fever with gatifloxacin vs. other options

Cost of treatment of enteric fever with gatifloxacin and several other antibiotics was estimated using data obtained from an on-line pharmacy database in India <http://chemistparadise.com>. Generally accepted dosage regimens for adults of 50 kg and 75 kg body weight, and children of 15 kg and 25 kg body weight were used to estimate the overall cost of treatment for these different classes. For gatifloxacin, the maximum daily dose was set at 600mg.

Table 10. Dose and duration of therapy of enteric fever with gatifloxacin and other regimens. Examples of total dose for a 15kg and 25kg child and a 50kg and 75kg adult are provided.

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg/kg/d)</th>
<th>Days</th>
<th>75 Kg (adult)</th>
<th>50 Kg (adult)</th>
<th>25 Kg (child)</th>
<th>15 Kg (child)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatifloxacin</td>
<td>10</td>
<td>7</td>
<td>600</td>
<td>500</td>
<td>250</td>
<td>150</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>75</td>
<td>14</td>
<td>5625</td>
<td>3750</td>
<td>1875</td>
<td>1125</td>
</tr>
<tr>
<td>Cefixime</td>
<td>20</td>
<td>14</td>
<td>1500</td>
<td>1000</td>
<td>500</td>
<td>300</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>20</td>
<td>14</td>
<td>4000</td>
<td>2000</td>
<td>2000</td>
<td>1000</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>20</td>
<td>7</td>
<td>1500</td>
<td>1000</td>
<td>500</td>
<td>300</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>20</td>
<td>7</td>
<td>1500</td>
<td>1000</td>
<td>500</td>
<td>300</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>7</td>
<td>1000</td>
<td>1000</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

All gatifloxacin products available in India on 1st November 2010 were identified, and per tablet costs obtained in US$. Similarly, the costs of chloramphenicol, ceftriaxone, ciprofloxacin, ofloxacin, and azithromycin were obtained. These were wholesale costs to pharmacy of single packs of, in general, 10 tablets. Since there were a large number of products available, with a wide price range, the mean cost was obtained for each compound and strength. Only solid dosage forms (capsule/tablet) were considered, although examination of the costs of specific paediatric formulations and parenteral formulations, where available, showed similar price structures. The mean single tablet costs were estimated, and applied to the different dosage regimens to give per treatment costs, using the most appropriate dose sizes for the different weight classes. The derived data (in US$) are tabulated below.
**Table 11. Cost of treating children and adults with enteric fever with gatifloxacin and other regimens**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost range per tablet</th>
<th>Mean cost per tablet</th>
<th>Cost for 75 kg Adult* ($)</th>
<th>Cost for 50 Kg Adult* ($)</th>
<th>Cost for 25 Kg Child* ($)</th>
<th>Cost for 15 Kg Child* ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatifloxacin 400</td>
<td>0.07-1.00</td>
<td>$0.55</td>
<td>$6.30</td>
<td>$5.25</td>
<td>$3.83</td>
<td>$2.44</td>
</tr>
<tr>
<td>Ciprofloxacin 500</td>
<td>0.09-0.81</td>
<td>$0.46</td>
<td>$12.96</td>
<td>$8.64</td>
<td>$4.32</td>
<td>$3.26</td>
</tr>
<tr>
<td>Azithromycin 250</td>
<td>0.09-3.28</td>
<td>$0.89</td>
<td>$18.47</td>
<td>$18.47</td>
<td>$12.40</td>
<td>$12.40</td>
</tr>
<tr>
<td>Ofloxacin 400</td>
<td>0.08-0.99</td>
<td>$0.62</td>
<td>$20.80</td>
<td>$14.00</td>
<td>$7.00</td>
<td>$5.00</td>
</tr>
<tr>
<td>Chloramphenicol 500</td>
<td>0.17-0.73</td>
<td>$0.38</td>
<td>$58.22</td>
<td>$38.48</td>
<td>$19.74</td>
<td>$11.84</td>
</tr>
<tr>
<td>Ceftriaxone 200</td>
<td>0.65</td>
<td>$0.65</td>
<td>$137.34</td>
<td>$91.56</td>
<td>$91.56</td>
<td>$56.00</td>
</tr>
<tr>
<td>Cefixime 200</td>
<td>0.08-4.08</td>
<td>$1.56</td>
<td>$163.50</td>
<td>$109.00</td>
<td>$54.50</td>
<td>$50.80</td>
</tr>
</tbody>
</table>

* usually half strength tablets/capsules used for these estimates

Gatifloxacin appears to be cheapest option. The next least expensive drug is ciprofloxacin, which is 13%-69% more expensive. Ofloxacin is 1.83-2.05 and azithromycin is 3-5 times as expensive. Chloramphenicol is 5-9 times as expensive. The most costly options are ceftriaxone (17-24) and cefixime (14-26) times as expensive.

**Figure 4. Comparative costs of treatment with gatifloxacin vs. other regimens for enteric fever (in the Table: relative costs, Gatifloxacin = 1)**

A very large number of products (often in excess of 100 alternatives for each dose formulation) are available, with widely differing costs, except for ceftriaxone where only a single product was listed. Costs for the better-known manufacturers were in general higher, but not always so. Although product costs have been estimated for treatments, this is a
basic analysis, and no attempt has been made to assess quality of product, which would be a significant factor in determining true cost and efficacy of treatment. While single tablet costs of other products are often lower than gatifloxacin, cost of treatment is determined by the regimen used, and when this is considered, the cost of gatifloxacin treatment, using Indian derived material, is lower than with other accepted treatments. Some limited data are available for other countries and roughly follows that of the Indian data (much of the material used is of Indian origin, especially in the sub-continent), but detailed information on costs of all products within a country are not available to allow a similar analysis.

12.3 Direct costs of treatment of enteric fever with gatifloxacin practical dosing

Using the anthropometric database of Nepalese and Vietnamese patients, and applying the practical dosing schedule with the current 200mg and 400mg tablets, we calculated the costs of treating 1,000 cases of enteric fever. These amount to 4,150 $. Using the Vietnamese patients’ profile, the projected cost of drug for treating all estimated ~4500 cases occurring in one year in Vietnam will cost ~15,800$.

Table 12. Cost of drug for treating 1000 enteric fever patients with gatifloxacin using the practical dosing schedule with the current non-scored 200mg and 400mg tablets

<table>
<thead>
<tr>
<th>body weight class (kg)</th>
<th>No. per 1000 pts</th>
<th>total No. tablets required</th>
<th>cost/Rx</th>
<th>cost/1000 Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15'</td>
<td>97</td>
<td>7 X 200mg</td>
<td>$2.66</td>
<td>$258.02</td>
</tr>
<tr>
<td>15 to 29</td>
<td>342</td>
<td>7 X 200mg</td>
<td>$2.66</td>
<td>$909.72</td>
</tr>
<tr>
<td>30 to 49</td>
<td>296</td>
<td>7 X 400mg</td>
<td>$4.06</td>
<td>$1,201.76</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>265</td>
<td>7 X 600mg</td>
<td>$6.72</td>
<td>$1,780.80</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1000</td>
<td></td>
<td></td>
<td>$4,150.30</td>
</tr>
</tbody>
</table>

When applying these calculations to Vietnam, the total costs of treating all the ~4500 cases per annum of the entire country will be ~15,800$ for drug costs.

Table 13. Cost of drug to treat all cases occurring in one year in Vietnam

<table>
<thead>
<tr>
<th>body weight class (kg)</th>
<th>% population</th>
<th>total No. tablets required</th>
<th>cost/1000 Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15'</td>
<td>14%</td>
<td>7 X 200mg</td>
<td>$1,671.79</td>
</tr>
<tr>
<td>15 to 29</td>
<td>49%</td>
<td>7 X 200mg</td>
<td>$5,817.82</td>
</tr>
<tr>
<td>30 to 49</td>
<td>25%</td>
<td>7 X 400mg</td>
<td>$4,593.02</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>12%</td>
<td>7 X 600mg</td>
<td>$3,716.65</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td>$15,799.27</td>
</tr>
</tbody>
</table>
12.4 **Total direct and indirect costs**

We are not in a position at present to submit a complete cost-effectiveness analysis. Cost of illness has not been entirely quantified for enteric fever. To account for all direct costs, we are collecting information on cost of care in Nepal and Vietnam. We are also attempting to collect more anthropometric data on enteric fever patients from different settings to generate more complete projections of the applicability of the practical dosing and costs of drug.

Using gatifloxacin will also mean that an antibiogram is not needed - this cost should also be factored in.

13 **Summary of regulatory status of the medicine**

Gatifloxacin was originally granted licences in the USA (Bristol-Myers Squibb) and Japan (Kyorin) in 1999. The indications included general infections sensitive to fluoroquinolones and community acquired pneumonia. In 2002, there were indications that some patients might suffer dysglycaemia, and warnings were added to the SPC. Following publication of a review of dysglycaemia related deaths (64) and an editorial (68) in March 2006 in NEJM, the US FDA required a ‘Black Box’ warning¹ to be added to the SPC. Subsequently, in May 2006, Bristol-Myers Squibb stopped manufacture of Tequin®. Similar action was taken in 2008 in Japan. In addition, The US FDA in September 2008 decided that, since "Tequin (gatifloxacin) Tablets, Injections and Oral Suspensions were withdrawn from sales for reasons of safety or effectiveness" gatifloxacin had become ineligible to the abbreviated new drug application (ANDA) should a new submission be filed for any of the previously approved dosage forms and indications of Tequin®(69).

Although the licence for oral products has not been renewed or has been voluntary withdrawn in countries such as the USA and Japan, the product remains approved in many countries where enteric fever is endemic and drug resistant strains are present - including India, Vietnam, Nepal, Bangladesh and China. It also remains widely available as an ophthalmic solution for eye infections.

14 **Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)**

A ‘Pending USP Standard’ was approved May 23 2008 (70). API and analytical standards exist in the Indian and Chinese Pharmacopoeias.

15 **Proposed (new) text for the WHO Model Formulary**

**Gatifloxacin**

*Tablet, 200mg, 400 mg (as sesqihydrate)*

<table>
<thead>
<tr>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatifloxacin is a synthetic fluoroquinolone that acts as a specific inhibitor of bacterial DNA gyrase and topoisomerase IV. It has a broad spectrum of efficacy against both Gram-</td>
</tr>
</tbody>
</table>

¹ The US Food and Drug Administration requires that - when serious adverse events are identified by the agency as being of particular concern - the drug’s printed materials carry a warning about those adverse effects surrounded by a printed black box - thus the name. As an example, since July 2008 fluoroquinolones as a family are required to have a black box warning for tendon rupture.
negative and Gram-positive aerobic bacteria. Transfer of genes containing DNA coding for antimicrobial resistance has been reported but as yet is of little clinical significance. Gatifloxacin is rapidly absorbed from the gastrointestinal tract. Peak plasma levels occur 1-2 hours after dosing. It is widely distributed in body tissues and concentrated in the bile. It has a plasma half-life of approximately 8 hours and is excreted in the urine mainly as unchanged drug. Elimination half-life 7-14 hours, with more than 70% of a given dose being excreted in 48 hours. Bioavailability 96%; protein binding 20%.

Clinical information

Uses
Treatment of typhoid and paratyphoid fever and infectious enteritis due to *Salmonella enteritidis*.

Dosage and administration
Children and adults: 10mg/kg orally (maximum 600mg/d) every 24 hours for 7 days.
A practical dosing with 200mg and 400mg strength tablets will be as follows:

<table>
<thead>
<tr>
<th>weight band</th>
<th>daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15kg</td>
<td>10mg/kg</td>
</tr>
<tr>
<td>15kg to 29kg</td>
<td>200mg</td>
</tr>
<tr>
<td>30kg to 49kg</td>
<td>400mg</td>
</tr>
<tr>
<td>&gt;= 50kg</td>
<td>600mg</td>
</tr>
</tbody>
</table>

Contraindications
- Hypersensitivity to any quinolone antibiotic.
- Diabetes mellitus.
- Pregnancy and lactation

Precautions
DISTURBANCES OF BLOOD GLUCOSE, INCLUDING SYMPTOMATIC HYPOGLYCEMIA AND HYPERGLYCEMIA, HAVE BEEN REPORTED WITH GATIFLOXACIN, USUALLY IN DIABETIC PATIENTS. HOWEVER, HYPOGLYCEMIA AND PARTICULARLY HYPERGLYCEMIA HAVE OCCURRED IN PATIENTS WITHOUT A HISTORY OF DIABETES. IN ADDITION TO DIABETES, OTHER RISK FACTORS ASSOCIATED WITH DYSGLYCEMIA WHILE TAKING GATIFLOXACIN INCLUDE OLDER AGE, RENAL INSUFFICIENCY AND CONCOMITANT GLUCOSE-ALTERING MEDICATIONS (PARTICULARLY HYPOGLYCEMIC MEDICATIONS). PATIENTS WITH THESE RISK FACTORS SHOULD BE CLOSELY MONITORED FOR GLUCOSE DISTURBANCES. IF SIGNS AND SYMPTOMS OF EITHER HYPOGLYCEMIA OR HYPERGLYCEMIA OCCUR IN ANY PATIENT BEING TREATED WITH TEQUIN, APPROPRIATE THERAPY MUST BE INITIATED IMMEDIATELY AND GATIFLOXACIN SHOULD BE DISCONTINUED.

Reduced dosage should be considered in patients with hepatic or renal impairment.

Gatifloxacin has the potential to prolong the QTc interval of the electrocardiogram in some individuals, with an increased risk of ventricular arrhythmias. Care should be taken in individuals taking Class 1A or Class 3 anti-arrhythmic agents.

Gatifloxacin has been rarely associated with tendon rupture, usually in elderly patients and those receiving corticosteroids.
Gatifloxacin should be administered cautiously to patients with epilepsy or raised intracranial pressure since seizures have been reported with other drugs of this class.

**Use in pregnancy and early childhood**
Gatifloxacin should not be used during pregnancy or during lactation. Use in children is controversial, since quinolones have been shown to induce arthropathy in the weightbearing joints of young animals. Although damage to growing cartilage has not been demonstrated in humans, use of quinolones is not generally recommended in children and adolescents. However, in severe infections such as enteric fever the benefits are considered to outweigh the risk.

**Adverse effects**
Gatifloxacin is generally well tolerated. The most frequently reported adverse effects are nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, headache, restlessness, tremor, confusion, rash, dizziness and pruritus.
Myalgia, tendinitis, and hepatic and renal disturbances have also been reported. Rapid heartbeat, mental confusion, hallucinations, agitation, nightmares, depression; photophobia; tendon rupture; insomnia, chills, fever; back pain; constipation, inflammation of the tongue, mouth sores; abnormal vision, ringing in the ears occur occasionally. Hyperosmolar nonketotic hyperglycaemic coma, diabetic ketoacidosis, and hypoglycaemic coma have been reported and are potentially fatal if untreated.

**Drug interactions**
Systemic exposure to gatifloxacin is increased with concomitant administration of probenicid and reduced with concomitant administration of oral iron compounds and antacids containing aluminium or magnesium salts. Significant interactions are not seen as a result of affects on major cytochrome P450 enzymes (3A, 1A2, 2C9, 2C19, and 2D6).

**Overdosage**
Gastric lavage is of value if performed promptly. Electrolyte balance must be maintained and cardiac function monitored. Serum concentrations of gatifloxacin may be lowered by dialysis.

**Storage**
Tablets should be stored in well-closed containers.
Gatifloxacin for enteric fever

APPENDICES

Appendix 1. Patent status
Appendix 2. Individual presentations of generic gatifloxacin in India
Appendix 3. ACCESS RESTRICTED TO REVIEWERS UNTIL PUBLISHED - Pharmacodynamics of gatifloxacin in patients with typhoid fever
Appendix 4. ACCESS RESTRICTED TO REVIEWERS UNTIL PUBLISHED - Population pharmacokinetics of gatifloxacin in south east Asian adult and pediatric patients with typhoid fever
Appendix 5. Updated Cochrane systematic review and meta-analysis of fluoroquinolones for enteric fever- will be submitted later
Appendix 6. ACCESS RESTRICTED TO REVIEWERS UNTIL PUBLISHED - A randomised controlled trial of gatifloxacin versus chloramphenicol for the treatment of uncomplicated enteric fever in Nepalese children and adults
Appendix 7. ACCESS RESTRICTED TO REVIEWERS UNTIL PUBLISHED - Blood glucose levels in pulmonary tuberculosis patients treated with gatifloxacin
REFERENCES

Gatifloxacin for enteric fever


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