PROPOSAL FOR
THE INCLUSION OF CEFIXIME IN
THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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1. Summary statement of the proposal for inclusion, change or deletion

Cefixime is proposed for inclusion in the WHO Model List of Essential Medicines for the treatment of uncomplicated sexually transmitted infections caused by *Neisseria gonorrhoeae* (*N. gonorrhoeae*).

Gonococcal infections occur worldwide and are the commonest cause of urethral discharge in men and they are predominantly asymptomatic in adult women and adolescent girls. These infections are responsible for complications such as pelvic inflammatory disease (PID), with consequences such as infertility, ectopic pregnancy and chronic pelvic pain. During pregnancy there may also be vertical transmission to the newborn, causing neonatal ophthalmia, which can cause blindness.

From one decade to the next, the treatment of gonorrhoea has been made difficult by the development of resistant strains.

Cefixime is a third generation cephalosporin which is administered as a single oral dose and has few, mild side effects. It is indicated for use in uncomplicated anogenital gonorrhoea caused by both penicillinase- and non- penicillinase producing *N. gonorrhoeae*. Recent studies show that it is also safe for use during pregnancy.

2. Name of focal point in WHO submitting or supporting the application

Dr. Francis Ndowa
Department of Reproductive Health and Research (RHR)
STI Team

3. Name of the Organization(s) consulted and/or supporting the application

World Health Organization (WHO)

4. International Non-proprietary Name (INN, generic) of the drug

CEFIXIME

5. Listing as an individual medicine or example as a therapeutic group

Cephalosporins are antibiotics that are divided into generations that differ in their spectrum of activity against bacterial infections. Cefixime is a semi-synthetic, amino-thiazolyl, broad spectrum, third generation cephalosporin. It has a plasma elimination half-life of 3 hours which is longer than that reported for other orally active cephalosporins which makes it effective as a single dose or once daily regimen.

The third generation cephalosporins which are already on the WHO Model List of Essential Medicines are ceftriaxone and ceftazidime. Both of these drugs are administered by injection, and only ceftriaxone is recommended in the WHO Guidelines for the Management of Sexually Transmitted Infections for the treatment of uncomplicated anogenital gonococcal infections. Cefixime would be included on the List for its use as an orally administered alternative in the single dose treatment of uncomplicated anogenital gonococcal infections.
6. Public health relevance (information on the disease burden, assessment of current use, target population)

*N. gonorrhoeae*, a Gram-negative diplococcus, is a common, curable cause of anogenital infections. Clinically, it presents as urethral discharge and epididymitis in men, and cervicitis in women. Complications of this infection include PID in women, the long term sequelae of which are infertility, ectopic pregnancy and chronic pelvic pain. Gonococcal infection of the eyes occurs in both adults and in about 30% of neonates born to an infected woman and can lead to blindness if not treated early and adequately.

In 1999 WHO estimated that 62 million new cases of gonorrhoea occur annually in adult men and women[1]. The regions most affected are sub-Saharan Africa, south and south-east Asia and Latin America and the Caribbean. Furthermore, the most marginalised people, in social and/or economic terms, are those that are most affected by this disease in all countries, with the more developed countries having much lower rates[2].

A number of studies have shown that gonorrhoea and other non-ulcerative STIs facilitate HIV infection, though not to the same degree as ulcerative STIs. In the case of gonorrhoea, both transmission and acquisition of HIV are increased [2-4].

Global antimicrobial resistance to penicillins, tetracyclines, macrolides and quinolones, drugs which have historically been used to treat this infection, has been of concern and a challenge in the management of gonorrhoea. Third generation cephalosporins such as ceftriaxone and cefixime have maintained their efficacy.

Strategies that enhance treatment compliance are particularly important for the treatment of STIs. Simplification of treatment is one of these. Single dose regimen for the treatment of gonorrhoea have the potential to improve compliance[5-7]. In addition, an oral formulation of a drug is an easier and cheaper route of administration than an injectable preparation. One of WHO's recommendations, as part of its policy to ensure adherence to universal precautions, is to avoid unnecessary injections and, where possible, prescribe oral equivalents.

Cefixime is also used for the treatment of infections other than gonorrhoea, including urinary tract infections, lower respiratory tract infections in the elderly, and otitis media in children. Its use in these diseases has been documented and, in most cases, requires single or multiple daily dosages over a period of 5-7 days. For gonorrhoea, however, the drug would be given as a single dose. The drug can also be safely administered to younger age groups such as adolescents and in pregnant women.
7. Treatment details (dosage regime; duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities or skills)

Clinical trials with different dosages of 200 mg, 400 mg and 800 mg have been conducted to determine the efficacy of cefixime against the gonococcus. The summary conclusions are that the lower dose of 200 mg runs the risk of selecting for resistant strains and as the 400 mg dose is effective and efficacious, the 800 mg dose would be unnecessarily expensive as well as needlessly increase gastrointestinal adverse effects. [5, 8].

WHO Guidelines for the Management of Sexually Transmitted Infections [9]
The choice of antimicrobials for STIs is guided by criteria which include:

- Drugs that have an efficacy of 95% or more. Regimens yielding cure rates between 85% and 95% may be used with caution but lower cure rates are unacceptable
- Resistance is unlikely to develop or likely to be delayed
- Have acceptable toxicity and tolerance
- Drugs that have an oral administration are favoured over parenteral drugs
- Single doses are preferred to multiple dose regimens.
- Drugs that can also be administered during pregnancy and lactation.

In the most recent WHO Guidelines for the Management of Sexually Transmitted Infections (2003) cefixime is recommended for uncomplicated gonococcal anogenital infections. The recommended dose is: Cefixime, 400 mg orally, as a single dose.

European STD Guidelines [10]
In these guidelines the recommendation for the treatment of gonorrhoea infections of the urethra, cervix and rectum is the same as the WHO guidelines, and includes cefixime 400 mg orally, as a single dose, as one of the first line options.

Centres for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines [11]
In the CDC guidelines under the section on uncomplicated gonococcal infections of the cervix, urethra and rectum, cefixime 400 mg is one of the first line treatment options.

Apart from standard training, the provision of this drug requires no special skills, no special diagnostic tests and no special treatment facilities. This means that it could be used at all levels of the health system, including primary health care (PHC) settings.

8. Summary of comparative effectiveness
Cefixime has been compared to other drugs within its class and to other drugs in general. The following comparisons are of interest for this proposal.

Cefixime is a non-ester cephalosporin and has different pharmacokinetics from some of the other cephalosporins. It has an extended half-life compared to other orally active cephalosporins[12], low rate of recovery in urine and is found in a high
concentration in the bile and in gall bladder tissue, indicating hepatic elimination[13, 14]. The absorption kinetics are not affected by the patient being either fasted or non-fasted[12, 13]. Dose adjustment appears not to be necessary in patients with renal insufficiency except in dialysis patients and non-dialysis patients with severe insufficiency[15]. There are no significant increases in the mean maximum plasma concentration in young or elderly subjects; thus, dosage adjustment due to age should not be necessary[12].

At the beginning of its use, cefixime was administered as an 800 mg dose. A study with 146 evaluable cases of gonorrhoea in men who were randomized in a 2:1 ratio to receive cefixime 800 mg or amoxicillin 3 g and probenicid 1 g found this dose of cefixime to cure 99% of uncomplicated gonococcal urethritis in men, compared to 96% cure rate found in those that were treated with amoxicillin and probencid[16]. Both regimes were ineffective against coexistent infection with *Chlamydia trachomatis* (*C.trachomatis*) and *Ureaplasma urealyticum*.

Cefixime, at either a dose of 400 mg or 800 mg single dose, was compared to ceftriaxone 250 mg in a randomized, unblinded multi-centre study of both men and women with uncomplicated gonorrhoea. The overall cure rates were similar in men and women and all three regimes were well tolerated. Thus, in the treatment of uncomplicated gonorrhoea either dosage level of cefixime was found to be as effective as the recommended regimen of ceftriaxone[17].

Another study on efficacy compared a single oral 400 mg dose of cefixime to a 250 mg single intramuscular dose of ceftriaxone for the treatment of *N.gonorrhoeae* urethritis in 190 men and cervicitis in 46 women. A bacteriologic cure was recorded in 100% of evaluable patients treated with ceftriaxone and 98% of evaluable patients treated with cefixime. The conclusion reached was that cefixime was an effective alternative for the treatment of uncomplicated gonococcal urethritis in men and cervicitis in women[18].

Cefixime has also been compared to other drugs used for the treatment of gonorrhoea which are not cephalosporins. Ciprofloxacin, a fluoroquinolone, has been an inexpensive, highly effective, oral treatment for this infection. It was also shown to be more effective in total gonococcal killing in human fallopian tube organ culture than cefixime[19]. However, the gradual increase of resistance to fluoroquinolones has rendered ciprofloxacin less and less effective against gonorrhoea in some areas. For example in the Philippines a randomized trial of ciprofloxacin compared to cefixime for the treatment of gonorrhoea showed that the organism was re-isolated within 28 days after treatment in 3.8% of women given cefixime compared to 32.3% of women given ciprofloxacin[20]. The development of resistance of *N. gonorrhoeae* to ciprofloxacin has also been reported in Singapore[21].

As the use of cefixime increases, it will be important to monitor the development of resistance. To date, only 3 cases of multidrug-resistant *N. gonorrhoeae* with decreased susceptibility to cefixime have been reported. These were in Hawaii(USA) in 2001[22].
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Study population</th>
<th>Cure rates</th>
<th>Outcome</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megran DW; Lefebvre K; Willets V et. al. Antimicob Agents Chemother. 1990 34(2): 355-7</td>
<td>Randomised study of single dose oral cefixime versus amoxicillin plus probenecid for treatment of uncomplicated gonorrhoea in men. (Lederle support)</td>
<td>146 men 18 years and older (Canada)</td>
<td>99% - cefixime 800 mg  96% - amoxicillin 3g and probenecid 1g</td>
<td>Cefixime well tolerated and easy to administer.</td>
<td></td>
</tr>
<tr>
<td>Handsfield HH; McCormack WM; Hook EW III et.al. N Engl J Med 1991, 325(19):1337-41</td>
<td>Randomized, unblinded multicentre study comparing a single dose of cefixime with ceftriaxone as treatment for uncomplicated gonorrhoea</td>
<td>209 men and 124 women (USA)</td>
<td>96% - cefixime 400 mg oral  98% - cefixime 800 mg oral  98% - ceftriaxone 250 mg im</td>
<td>Cure rates similar in men and women. All three regimes well tolerated.</td>
<td></td>
</tr>
<tr>
<td>Plourde PJ; Tyndall M; Agoki E et. al. J Infect Dis 1992, 166(4):919-22</td>
<td>Randomised study comparing single dose cefixime with single dose ceftriaxone in the treatment of antimicrobial-resistant neisseria gonorrhoea.</td>
<td>236 patients - male and female (Kenya)</td>
<td>98% - eradication cefixime 400mg oral  100% - eradication ceftriaxone 250mg im</td>
<td>Cefixime was highly effective in eradicating antimicrobial-resistant uncomplicated gonococcal infection from the urethra and cervix.</td>
<td>Advantage of cefixime is oral administration, use in pharyngeal gonorrhoea and in children and pregnant women.</td>
</tr>
<tr>
<td>Aplasca de Los Reyes MR; Pato-Mesola V; Klausner JD et. al. Clin Infect Dis 2001, 32(9):1313-8</td>
<td>Randomized (Bayer and Lederle support)</td>
<td>105 female sex workers (The Philippines)</td>
<td>3.8% - treatment failure cefixime 400 mg  32.3% - treatment failure ciprofloxacin 500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Trials</td>
<td>Patients</td>
<td>Efficacy</td>
<td>Differences</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ramus RM; Sheffield JS; Mayfield JA et. al.</td>
<td>Randomised trial comparing oral cefixime and intramuscular ceftriaxone for treatment of gonorrhoea in pregnancy.</td>
<td>161 patients (USA)</td>
<td>95% - overall efficacy 95% - effectiveness of ceftriaxone 125 mg 96% - effectiveness of cefixime 400 mg</td>
<td>No significant difference noted in overall efficacy or by site of infection.</td>
<td></td>
</tr>
<tr>
<td>Portilla I; Lutz B; Montalvo M et. al.</td>
<td>Randomised trial</td>
<td>75 men, 150 women (USA)</td>
<td>97% - bacteria eradication cefixime 400 mg/800 mg 100% bacterial eradication ceftriaxone 250 mg</td>
<td>Cefixime as well tolerated and efficacious as ceftriaxone. Adverse experiences with cefixime - 10%, self-limiting. No adverse experiences with ceftriaxone.</td>
<td></td>
</tr>
</tbody>
</table>
9. Summary of comparative evidence on safety

Estimate of total patient exposure to date
A review conducted in the US on the data on the use of cefixime collected worldwide from clinical trials and post-marketing studies in a (combined) total of 42,000 persons treated with cefixime showed that the adverse effects experienced were similar in adults and children in all groups [23].

A study was conducted in England comparing the results of five observational cohort studies which examined the safety of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime. Each study looked at one of these drugs and the final cohort size for each of these drugs was more than 11,000. The observational cohorts were conducted by Prescription Event Monitoring (PEM). Cefixime was used in patients with respiratory tract infections, urinary tract infections and for a wide variety of other infections. The children in this cohort included those less than 10 years of age, treated mainly for respiratory tract and ear infections. For this variety of illnesses, the dosages varied from 75 mg to 800 mg per day. It was not stated which, if any, were single dose treatments[24].

Issues related to pregnancy
Gonococcal infection is a major contributor to adverse outcomes of pregnancy[25]. Infections which occur early in pregnancy may cause septic abortions while those occurring later in pregnancy may cause prematurity or low birth weight. The infection may also be responsible for ophthalmia in neonates, which is a frequent and severe complication[26].

Cefixime was originally classified in Pregnancy category B1. A recent Cochrane review on antibiotics for gonorrhoea used in pregnancy found that ceftriaxone and cefixime were similar in effect and in the side effects as well[27]. However, the number of women in each of the studies has, so far, been small.

One such study in the USA was conducted among 161 pregnant women who underwent pretreatment endo-cervical, oral and anal cultures for N. gonorrhoeae. This prospective clinical trial used cefixime at 400 mg and ceftriaxone at 125 mg (having been reduced from 250 mg in the two most recent STI management guidelines by CDC and WHO). This dosage of cefixime had been found to be effective in men and nonpregnant women but was thought to be sub-therapeutic in pregnancy due to increased volume of distribution, increased glomerular filtration rate and decreased gastric motility. No significant difference was noted between the two drugs in the overall efficacy or by the site of the infection. It was concluded that both intramuscular ceftriaxone 125 mg and oral cefixime 400 mg appear to be effective for the treatment of gonococcal infection in pregnancy[28].

In addition, a review of the treatment options for sexually transmitted bacterial diseases in pregnant women found that a single dose of cefixime 400 mg is considered

\[1\] Pregnancy category B - found safe in animals, no human data
safe during pregnancy and, being an oral equivalent of intramuscular ceftriaxone, can be viewed as the treatment of choice[29].

**Adverse effects**

The drug is as well tolerated and efficacious as ceftriaxone in patients with urethritis and cervicitis[31]. Most of the side effects of cefixime are related to the gastrointestinal system. These are described as transient and mild to moderate in severity, consisting of soft or loose stools (as distinct from diarrhoea), abdominal pain, dyspepsia, nausea and vomiting. Diarrhoea was moderate to severe in less than 10% of both adults and children. The onset of diarrhoea was within 4 days of beginning the treatment[12].

In the large observational cohort study of more than 11000 patients referred to above, six events were reported as adverse reactions to cefixime - three of pseudo-membranous colitis, one of which was fatal; erythema multiforme; and one urticaria[24]. Nausea and vomiting were common to all the drugs in the study.

Symptoms of drug hypersensitivity were infrequently reported especially among patients who had had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. Cross hypersensitivity has been documented in up to 10% of patients with a history of penicillin allergy.

In general, the cephalosporins most effective against *N. gonorrhoeae* are safe and well tolerated but cefixime is one of only three that can be given orally. The others are not recommended for gonorrhoea treatment[32].

10. **Summary of available data on comparative cost and cost-effectiveness within therapeutical group**

In a study which reviewed price trends for prescription pharmaceuticals conducted in the US from 1995-1999 third generation cephalosporins were actually priced lower than the earlier generations. However, by the end of the study period they were priced similarly[33].

The current prices available for the individual drugs are shown in tables 2 and 3. The course used for treatment of gonorrhoea for this table is 400 mg orally as a single dose. For ceftriaxone it is 125 mg as an intramuscular injection, single dose.
Table 2. Cefixime prices

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>company</th>
<th>Unit cost</th>
<th>Cost per course - local currency</th>
<th>Cost per course - US$</th>
<th>Source of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprax</td>
<td>Rhone-Poulenc Rorer</td>
<td>7-tab pack £ 12.03</td>
<td>£ 3.44</td>
<td>$ 5.83</td>
<td>BNF²</td>
</tr>
<tr>
<td>Suprax</td>
<td></td>
<td>Can$ 3.09</td>
<td>Can$ 3.09</td>
<td>$ 2.36</td>
<td>Ontario Drug Benefit Formulary³</td>
</tr>
<tr>
<td>Cefixime</td>
<td></td>
<td>not available</td>
<td>not available</td>
<td>$ 4.14</td>
<td>Outlook⁴</td>
</tr>
<tr>
<td>Neo Cefix</td>
<td>Neoquimica</td>
<td>5-tab pack R$ 53.24</td>
<td>R$ 10.65</td>
<td>$ 3.71</td>
<td>J N Moura Informatica⁵</td>
</tr>
<tr>
<td>Tocef</td>
<td>General</td>
<td>4-cap pack Taka 80.00</td>
<td>Taka 80.00</td>
<td>$ 1.38</td>
<td>Drug Bangladesh⁶</td>
</tr>
<tr>
<td>T-Cef</td>
<td>Drug</td>
<td>8-cap pack Taka 360.00</td>
<td>Taka 80.00</td>
<td>$ 1.38</td>
<td>Drug Bangladesh</td>
</tr>
<tr>
<td>Triocim</td>
<td>Beximco</td>
<td>12 cap pack Taka 600.00</td>
<td>Taka 100.00</td>
<td>$ 1.73</td>
<td>Drug Bangladesh</td>
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</tbody>
</table>

Table 3. Ceftriaxone prices

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>company</th>
<th>Unit cost</th>
<th>Cost per course - local currency</th>
<th>Cost per course - US$</th>
<th>Source of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocephin</td>
<td>Roche</td>
<td>250 mg vial £ 2.74</td>
<td>£ 1.37</td>
<td>$ 2.32</td>
<td>BNF⁷</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>1 g vial £ 9.95</td>
<td>£ 1.24</td>
<td>$ 2.11</td>
<td>BNF</td>
</tr>
<tr>
<td>Rocephin</td>
<td></td>
<td>250 mg vial Can$ 10.75</td>
<td>Can$ 5.38</td>
<td>$ 4.11</td>
<td>Ontario Drug Benefit Formulary⁸</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>1 g vial US$ 1.29</td>
<td>US$ 1.29</td>
<td>$ 0.16</td>
<td>IDA¹</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>500 mg vial US$1.00</td>
<td>US$ 1.00</td>
<td>$ 0.13</td>
<td>IDA</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>250 mg vial US$ 1.02</td>
<td>US$ 1.02</td>
<td>$ 0.51</td>
<td>IDA</td>
</tr>
</tbody>
</table>

1 US $ = £ 0.59   1 US $ = Taka 57.88
1 US $ = Can $1.31 1 US $ = Real 2.87
Currency conversion rates are as of 28 Oct 2003.

⁵ www.jnmoura.com.br
⁶ www.drugbangladesh.com
⁹ International Dispensary Association (IDA)  http://erc.msh.org
A study of cost-effectiveness of management strategies for acute urethritis in the developing world used a model to assess the cost effectiveness of 3 urethritis management strategies in a theoretical cohort of 1000 men with urethral discharge syndrome. The three strategies were as follows: (1) all patients treated with cefixime for gonococcal urethritis (GU) and doxycycline for nongonococcal urethritis (NGU); (2) all patients treated with doxycycline for nongonococcal urethritis (NGU) and treated with cefixime based on direct microscopy of urethral smear and (3) all patients treated with cotrimoxazole or kanamycin for gonococcal urethritis and doxycycline for NGU.

The first strategy was the most effective but also the most expensive; the second saved money and drugs but was only valuable when laboratory performance was optimal; and the third was the least expensive but of limited effectiveness due to low follow-up visit rate, poor treatment compliance or lower drug efficacy. The conclusion from this modelling was that for an approach to be cost-effective, it would need to treat gonorrhoea with a single dose antibiotic from locally available products that cost no more than US$ 1.50[34].

Another study done on the cost-effective treatment of uncomplicated gonorrhoea including co-infection with *chlamydia trachomatis* showed that ceftriaxone yielded the lowest cost per cured patient, regardless of the prevalence of chlamydial genital infection as compared to cefixime and ciprofloxacin[35]. However, the major disadvantage of ceftriaxone is that it has to be administered intramuscularly and, generally, it is not sold in units of less than 250 mg and, thus, is relatively expensive at, and less cost-effective for, low volume use. In addition, if the cost of administering the injection is high, cefixime being an oral drug is an advantage. Though ciprofloxacin is also an oral drug its disadvantage is that there is increased antimicrobial resistance to it.

11. Summary of regulatory status
The patent for this drug expired in November 2002 and the company which held the patent (Wyeth, in the USA) has discontinued its manufacture. The drug is approved in Bangladesh, Brazil, Canada, France, the United Kingdom of Great Britain and Northern Ireland and the United States of America.

12. Pharmacopoeial standards
Cefixime is in both the United States Pharmacopoeia (USP) and the European Pharmacopoeia (PhEur). (Application submitted for entry in the International Pharmacopoeia).

*General information*
Cefixime is an oral formulation of third generation cephalosporins used in the treatment of uncomplicated anogenital gonorrhoea.

*Indication for use*
The single dose treatment of uncomplicated anogenital *N. gonorrhoea* infections.
Dosage and administration
Uncomplicated gonorrhoea, by mouth, ADULT and ADOLESCENT 12 years and older cefixime 400mg orally.

Contraindications
Cephalosporin hypersensitivity.

Precautions
Penicillin sensitivity (see section on beta-lactams), renal impairment (see appendix on renal impairment), pregnancy and breastfeeding (see appendix on pregnancy and breastfeeding).

Adverse effects
Diarrhoea, abdominal pain, dyspepsia, nausea and vomiting which are usually transient and mild. Diarrhoea is moderate to severe in less than 10% of adults. Rarely, erythema multiforme and urticaria, and pseudo-membranous colitis.
References