

# **Application for addition of 1g form of ceftriaxone to the complementary list of the WHO model list of essential medicines**

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# APPLICATION FOR ADDITION OF 1 GRAM DOSAGE FORM OF CEFTRIAXONE TO THE COMPLEMENTARY LIST OF THE WHO MODEL LIST OF ESSENTIAL MEDICINES

## 1. General

A request is made to add a 1 gram vial formulation of ceftriaxone to the complementary list of the WHO Model List of Essential Medicines for the treatment of epidemic bacterial meningitis due to meningococcus infection because availability of oily chloramphenicol is not assured.

- Name of the focal point in WHO submitting the application  
Dr William Perea, WHO/CDS/GAR (tel: +4122 791 1618).
- Name of the organization(s) consulted and/or supporting the application  
Médecins Sans Frontières (France) and Epicentre
- International Nonproprietary Name (INN, generic name) of the medicine  
Ceftriaxone (rINN, BAN, USAN)
- Whether listing is requested as an individual medicine or as an example of a therapeutic group  
Ceftriaxone is already listed as an individual medicine on the complementary list of the WHO Model List of Essential Medicines.

## 2. Information supporting the public health relevance

### 2.1 Bacterial Meningitis

Incidence: at least 1.2 million cases of meningitis occur worldwide each year, with 700,000 of these cases related to meningococcus in the past 10 years. (ref: World Health Organization. *Global surveillance of epidemic-prone infectious diseases*. Geneva: WHO 2000). In the non-epidemic context, meningococcus and pneumococcus account for the vast majority of cases of bacterial meningitis in patients over the age of 3 years. In children between 2 months and 3 years, *Streptococcus pneumoniae* and *Haemophilus influenzae* are causative agents along with *Neisseria meningitidis*. In very young infants under the age of 2 months, *Escherichia coli*, *Listeria monocytogenes*, *Salmonella spp*, and group B streptococcus are causative agents. Of the 135 000 estimated deaths related to bacterial meningitis each year, some 50 000 deaths are attributable to meningococcus (ref. WHO/EMC/BAC/98.3 <http://www.who.int/emc-documents/meningitis/whoemcbac983c.html> ).

In non-epidemic situations, meningitis occurs most often in pre-school children between 3 – 5 years old. While in epidemic situations, the maximal incidence is in older children between 5 – 10 years old, often extending to young adults. Military recruits and other individuals living in close quarters are at higher risk of getting meningitis. Close contacts have a 500 – 800 higher risk of developing bacterial meningitis. Secondary attack rates are 4 per 1000. Chemoprophylaxis with either rifampicin, spiramycin, or ciprofloxacin is recommended to prevent secondary infection. Vaccines are available for Meningococcus types A and C as well as *H. influenzae* type b. Meningococcal Meningitis is a serious life threatening illness with mortality rates of 10% and neurological sequelae in 10 – 20% of patients. (ref. WHO/EMC/BAC/98.3).

## 2.2 Epidemic Meningitis

In epidemic meningitis, meningococcus types A, C or W135 account for the vast majority of cases in patients over one year of age. Epidemics tend to occur in sub-saharan Africa during the dry season. For children under 1 year of age, other causative agents can contribute to epidemic meningitis.

In cases of African epidemics, attack rates can reach as high as 1,000 / 100,000 locally and up to 800 / 100,000 on a national scale in a very short period of time. In high risk zones during the dry season, the critical threshold used to define an outbreak is 15 cases / 100,000 people / week. Epidemics tend to occur during the dry season in sub-Saharan Africa with major epidemics having a periodicity of 8 – 12 years. The last major epidemic occurred in this area in 1996 – 1997 (ref. WHO/EMC/BAC/98.3).

Clinical signs in adults and children over the age of 1 year include: fever, severe headache, neck stiffness accompanied by Brudzinski's sign and Kernig's sign. Severe forms can present with coma, convulsions, neurological focal signs and purpura fulminans.

In children under one year of age, classic signs of meningitis are often absent. In such cases, refusal to eat, fever, diarrhoea, vomiting, drowsiness, along with seizures, and bulging fontanelles can all be indications to suspect a diagnosis of meningitis.

Laboratory evaluation involves a lumbar puncture with examination of the cerebrospinal fluid (CSF). Bacterial meningitis will produce cloudy CSF with greater than 500 Polymorphonuclear cells and a positive Pandy's test (protein in CSF), gram stain shows gram negative organisms while rapid latex tests for detection of bacterial antigens are available. In an epidemic context, once the meningococcal etiology has been confirmed for the epidemic, there is no need for routine lumbar puncture of new cases. (ref: Wall, R., Meningococcal disease: treatment and prevention, Annals of Medicine, 34(7-8):624-634, 2002).

## 3. Treatment details

*This section summarizes treatment of meningococcal meningitis and summarizes WHO treatment guidelines as well as diagnostic tests and syndromic management of epidemic meningitis.*

### 3.1 Antibiotic therapy in Meningococcal Meningitis

Ceftriaxone is effective at a dose of 50 – 100mg/kg/d IM against the most common causative agents of bacterial meningitis (pneumococcus, meningococcus and hemophilus influenza). The adult dose of ceftriaxone for epidemic meningitis varies between 2 – 4 g given in two injections IM. A major advantage over oily chloramphenicol is the clinical efficacy of single-dose ceftriaxone in sterilizing cerebrospinal fluid within 24 hours. (ref: Scholtz, H., Hofmann T., Noack R., Edwards, DJ, Stoeckel K. Prospective comparison of Ceftriaxone and Cefotaxime for the short term treatment of bacterial meningitis in children. *Chemotherapy* 1998; **44**: 142-147.)(ref: Cadoz M., Denis F, Guerma T, Prince-David M., Diop Mar I. Bacteriological pharmacological and clinical comparison between amoxicillin and ceftriaxone in the treatment of 300 purulent meningitis. *Path Biol* 1982; 30 (6): 522-5.)

An additional advantage includes a well-tolerated adverse-effect profile. Alternative treatments include oral amoxicillin and intravenous ampicillin given over a period of 5 days, although there is a much greater incidence of resistance to these agents. (ref: Wall, R., Meningococcal disease: treatment and prevention, *Annals of Medicine*, 34(7-8):624-634, 2002).

In developing countries, intramuscular oily chloramphenicol has been the recommended first line treatment for epidemic bacterial meningitis since 1976 because it can be given as a single dose (since 1995), is relatively cheap and has few other indications thereby limiting the possibility of development of widespread bacterial resistance. (ref: World Health Organization. Control of epidemic meningococcal disease. WHO practical guidelines. Ed. Fondation Marcel Mérieux, Lyon, France. 1995)(ref: Rey M, Ouedraogo L, Saliou F, et al. *Le traitement minute de la méningite cérébrospinale épidémique par injection intramusculaire unique de chloramphénicol. Médecine et Maladies Infectieuses* 1976; 6:120-24) (Saliou F, Ouedraogo L, Muslin D, Rey M. *L'injection unique de chloramphénicol dans le traitement de la méningite cérébrospinale en Afrique tropicale. Med Trop* 1977; 37: 2:141-7). But there are other formulations of chloramphenicol which appear for 23 different conditions in WHO treatment guidelines. According to Médecins Sans Frontières France and WHO, there are currently problems with production of oily chloramphenicol, with only one generic producer still manufacturing the drug after the principal manufacturer ceased production in March 2003. In addition, it is not as effective in sterilizing the CSF and has a higher incidence of side effects than ceftriaxone and cannot be given to pregnant or lactating females. Oily chloramphenicol is not recommended for use in infants under 2 months of age (ref. WHO/EMC/BAC/98.3).

Ceftriaxone is the recommended treatment for bacterial meningitis in many developed countries. Up until recently, it had been considered as an alternative treatment for bacterial meningitis in most age groups in developing countries due to the high cost of the patented molecule. Now that the patent has expired in several countries, generic versions are available which make it even less expensive to administer than chloramphenicol (see section 10). It is better tolerated, has fewer side effects, and is more effective bacteriologically when measuring sterilisation of CSF at 24 hours. There is a concern that widespread availability of low cost ceftriaxone in developing countries may lead to rapid emergence of resistance given that this drug can be used for several other indications, notably for the treatment of *Neisseria gonorrhoea* and other common pathogens. It is for this reason that we propose that the drug remains on the complementary List of the WHO Model List of Essential Medicines.

Comprehensive reviews on ceftriaxone have been published since the mid 1980's with over 580 references cited in the literature, including specific reviews on paediatric patients and meningitis patients (Ref: Wall, R., Meningococcal disease: treatment and prevention, *Annals of Medicine* 34: 624-634 , 2002). Other review articles discuss the selection of the safety and efficacy of this antibiotic. This information is already on file with WHO/EDM as part of the original submission for inclusion of ceftriaxone onto the Model List of Essential Medicines and will not be reproduced in this submission. Three articles are attached to this application to support inclusion of the 1 gram dosage form and the single dose treatment recommendation for epidemic bacterial meningitis (see section 7.2.4).

### 3.1.1. WHO Guidelines

The current WHO guidelines (ref: document WHO/EMC/BAC/98.3 available at <http://www.who.int/emc-documents/meningitis/whoemcbac983c.html>) recommend either:

- oily chloramphenicol 100 mg / kg / d IM, daily as single dose with possibility of repeating in 24 – 48 in case of relapse, max dose is 3 g, OR
- ceftriaxone 50 - 80 mg/kg/d IM, in a single dose with possibility of repeating in 24 – 48 in case of relapse, max dose is 2 - 4g

Alternative regimens are:

- amoxicillin PO, or ampicillin IV for 5 days

Ceftriaxone has the clear advantage that it is easy to administer (just 1 single dose), more effective at sterilizing the CSF and better tolerated than chloramphenicol; it is also less expensive than oily chloramphenicol now that it is available in generic form. Ceftriaxone is the recommended first line treatment for pregnant and lactating women as well as children aged 2 months to 1 year of age (ref: Management of epidemic meningococcal meningitis, 3<sup>rd</sup> edition, Medecins Sans Frontieres, 2004).

At the same time, there is a caveat about widespread and indiscriminate use of ceftriaxone which could lead to emergence of resistance which has been seen in the developed world. In addition, ceftriaxone will probably be used for treating common infectious conditions such as sexually transmitted diseases, thus making it difficult to have emergency stocks available at district level when meningitis epidemics occur.

Oily chloramphenicol is effective, well accepted and currently in widespread use in developing countries. It is therefore very important to have two effective antibiotics available for this serious illness in case of stock outs or production problems which might limit access to a particular medicine. It is for this reason that the international treatment guidelines still recommend oily chloramphenicol as the treatment of choice for resource limited settings with ceftriaxone as an alternative.(ref: Duke, T., Michael, A, et al., Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries? Arch Dis Child 2003;88:536-539 and Management of epidemic meningococcal meningitis, 3<sup>rd</sup> edition, Médecins Sans Frontières, 2004).

We propose at this time that both oily chloramphenicol and 1 g ceftriaxone should be included on the Model List of Essential Medicines.

### 3.1.2. Diagnostic tests for meningococcal meningitis

There are often no obvious clinical manifestations of meningococcal infection with asymptomatic nasal carriage being common. Meningitis caused by meningococcus is more readily diagnosable because of the following telltale clinical signs: rapid onset of fever, nuchal rigidity and altered sensorium. Spinal tap examination of the cerebrospinal fluid will reveal a turbulent CSF along with the presence of gram negative organisms as well as polymorphonuclear cells and protein. Culture of the CSF will confirm the presence of meningococcus. A rapid latex antigen test is also available.

### 3.1.3. Syndromic treatment of epidemic meningitis

In situations of epidemic meningitis (defined as more than 15 new cases / 100,000 people / week), meningococcus is the presumed causative agent and presumptive treatment with ceftriaxone or chloramphenicol is initiated promptly. Ceftriaxone has been shown to be effective in the empiric treatment of epidemic bacterial meningitis (ref: Duke T., Michael A, Mokela D, Wal T, Reeder J., Chloramphenicol or ceftriaxone or both, as treatment for meningitis in developing countries? *Arch Dis Child* 2003;88:536-539).

If a specific diagnosis is not possible, as is often the case in epidemic situations, patients should be treated using the syndromic approach. Clinical criteria for diagnosis of epidemic meningitis are listed above and further elaborated in the WHO and MSF guidelines on management of bacterial meningitis.

### 3.1.4. Studies

Three studies are provided to support the scientific basis for this application. The first study was conducted by Marhoum El Filali and colleagues in Morocco and published in 1993. Thirty-six patients were allocated in a randomised fashion to a treatment group consisting of either ceftriaxone 2g once daily for two days or a then standard regimen of benzylpenicillin (penicillin G) for 6 days. The study concluded that short term treatment with ceftriaxone is feasible (ref: Marhoum el Filali, K., Noun, M., et al. Ceftriaxone versus Penicillin G in the Short Term Treatment of Meningococcal Meningitis in Adults, *Eur. J. Clin.Microbiol.Infect. Dis.*, (12)10, 766-768 (1993).

**Study 1: Study of ceftriaxone 2g i.v. per day for 2 days compared to penicillin G 300, 000 IU/kg/d four times / d for 6 days conducted in Casablanca, Morocco, 1989 – 1990 (Marhoum El filali, et al, 1993)**

	ceftriaxone (n=16)	penicillin G (n=20)	p value
Mean time to apyrexia (+/-SD)(1)	3.1 +/- 1.4	3.8 +/- 1.8	NS
Mean time to disappearance of meningeal signs (days, +/- SD)	4.4 +/- 1.5	3.9 +/- 1.9	NS
Mean time to recovery of consciousness (days, +/- SD)	3.7 +/- 2.1	3.3 +/- 1.1	NS

(1) SD = standard deviation

A second study by MSF France was conducted in Niger and Mali between 1991 – 1995 in children hospitalised with a confirmed diagnosis of bacterial meningitis. Three hundred children were randomly assigned to either ceftriaxone for 2 days or long acting chloramphenicol for 2 days. The study concluded that in hospitals where resources were scarce and compliance to long treatment difficult to achieve, short treatment with ceftriaxone should be preferred to treat bacterial meningitis in children. At the same time it recommended that oily chloramphenicol should still be recommended as the first line treatment for bacterial meningitis. ([ref: Pecoul, B., Keita, M., et al., Ceftriaxone versus long-acting chloramphenicol for treatment of bacterial meningitis in children aged 2 – 35 months, 2004](#)). ([Permission from MSF to publish this document](#))

**Study 2: Study of ceftriaxone 75 mg/kg/d x 2 days versus long acting oily chloramphenicol 100mg/kg/d x 2d for Bacterial Meningitis conducted by MSF France in Mali and Niger, 1991 – 1995 (Pecoul, et al., submitted for publication)**

	ceftriaxone (n=157)	oily chloramphenicol (n=143)	Relative Risk (95% confidence interval)
Case Fatality Ratio at 72h	18.5%	21.7%	1.2 (0.7-1.8)
Clinical Tx Failure at 72h	29.9%	38.5%	1.3 (0.9-1.8)

The third study conducted by MSF France and Epicentre in Niger during a meningitis epidemic in 2003. Five hundred and three patients were randomised to received either ceftriaxone or oily chloramphenicol as a single injection with a second dose given after 24 – 48 hours in case of clinical failure. The case fatality rates, proportion of clinical failures and proportion of second injection and treatment sequelae were similar in both groups. The study showed equivalence between the two treatment groups for confirmed meningococcal meningitis. They concluded that ceftriaxone represents an equivalent alternative to chloramphenicol for the treatment of meningococcal meningitis during epidemics in resource poor settings. However they expressed concern about the possibility of rapid emergence of resistance if use is not monitored. ([ref: Nathan, N., Borel, T., et al, Traitement court de la méningite à méningocoques, essai clinique d'équivalence comparant le chloramphénicol en suspension huileuse à la ceftriaxone en 1 ou 2 injections, , MSF France, Epicentre Rapport final 2003](#)).

**Study 3: Niger study of ceftriaxone 100 mg/kg/d single treatment versus oily chloramphenicol 100mg / kg / d single treatment conducted by MSF France, Epicentre and Ministry of Health of Niger, 2003 (Nathan, et al.)**

	Ceftriaxone (n=251)	Oily Chloramphenicol (n=259)	Stat Signif
Intention to Treat Analysis	8.9%	8.6%	NS
Clinical Tx Failure rate at 72h			
Death at 72h	5.7%	4.7%	NS
Need for 2 <sup>nd</sup> injection	6.8%	7.7%	NS
Sequelae	6.9%	5.3%	NS
Per Protocol Analysis	5.0%	5.4%	NS
Clinical Tx Failure rate at 72h			
Death at 72h	3.8%	3.4%	NS
Need for 2 <sup>nd</sup> injection	7.1%	6.3%	NS
Sequelae	9.1%	6.3%	NS

#### **4. Summary of comparative effectiveness in a variety of clinical settings**

Ceftriaxone has already been previously reviewed by the WHO Expert Committee on the Use of Essential Medicines in 1995 and is currently included on the complementary list of essential medicines. This application focuses on adding the 1g vial form and a change of indication of ceftriaxone to include short course treatment of epidemic bacterial meningitis.

##### **4.1. Identification of clinical evidence**

The attached studies provide scientific evidence of ceftriaxone's effectiveness in the treatment of epidemic meningococcal meningitis.

##### **4.2. Summary of available data**

Ceftriaxone is an effective treatment for epidemic meningococcal meningitis.

#### **4.3. Summary of available estimates of comparative effectiveness**

The most recent studies by MSF France and Epicentre (attached to this application) show that short course ceftriaxone is equally effective to oily chloramphenicol for the treatment of epidemic meningococcal meningitis

#### **5. Summary of comparative evidence on safety**

Ceftriaxone is approved by US FDA and EMEA and is already widely available in the developing World. In addition, it is on the WHO Model List of Essential Medicines.

##### **5.1. Estimate of total patient exposure to date**

Experience with ceftriaxone is substantial over almost 2 decades.

##### **5.2. Description of adverse effects/reactions**

This information is already included in the WHO Model Formulary

##### **5.3. Summary of comparative safety against comparators**

Compared to oily chloramphenicol, ceftriaxone has fewer side-effects and can be used in pregnant women and younger children. Information is already available in WHO and MSF guidelines.

#### **6. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group**

##### **6.1. Range of costs of the proposed medicine**

Ceftriaxone is available from 3 sources in India, France and Israel with prices ranging from USD \$0.839 to \$1.82 for a 1 g vial. (Ref: Sources and Prices of Selected Medicines and Diagnostics for people living with HIV/AIDS, published by WHO, UNAIDS, MSF and UNICEF, June 2003). According to MSF, oily chloramphenicol currently costs between \$1.20 - \$1.50 for a 500mg vial from the sole remaining supplier, Gland Pharma, India.

### Comparison of costs per gram of ceftriaxone 1g versus oily chloramphenicol

Drug	Range of costs per gram (in USD)	# of generic producers	Tx cost
ceftriaxone (1)	0.84 – 1.82	3	1.68 – 3.64
chloramphenicol (2)	2.40 – 3.00	1	4.80 – 6.00

(1) Source: Sources and Prices of Selected Medicines and Diagnostics for People living with HIV/AIDS, WHO, UNAIDS, MSF and UNICEF, June 2003.

(2) Source: International Dispensary Association, May 2004.

## 6.2 Comparative cost-effectiveness presented as range of cost per routine outcome

Average treatment dose for oily chloramphenicol is 2g single injection at a cost of USD \$4.80 - \$6.00. Average treatment dose for ceftriaxone is also 2g single injection at a cost of USD \$1.68 - \$3.64. A single injection of either antibiotic leads to cure in the majority of cases according to the studies that are included with this application.

## 7. Summary of regulatory status of the medicine

The 1g formulation of ceftriaxone is registered in Europe and the USA and is widely available in developing countries at this time.

## 8. Availability of pharmacopoeial standards

USP, British Pharmacopoea, WHO/CDS has requested that ceftriaxone be added to the International Pharmacopoea.

## 9. Proposed text for the WHO Model Formulary:

*It is proposed to add the following text in the section entitled "Dose":*

*Epidemic bacterial meningitis due to N. meningitides, ADULT single treatment by deep intramuscular injection, 2 – 4 g; CHILD single treatment by deep intramuscular injection, 100 mg / kg, repeat treatment at a dose of 75 mg/kg in 24 – 48 hours if no clinical improvement*

## References

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