

**10<sup>th</sup> Invitation to manufacturers of medicinal products  
for HIV infection and related diseases  
to submit an Expression of Interest (EOI) for product evaluation to the  
WHO Prequalification of Medicines Programme**  
(November 2010)

To support national and global efforts to increase access to and the affordability of HIV/AIDS-related care and treatment, WHO, together with UNICEF, UNAIDS and UNITAID, invite manufacturers of selected pharmaceutical products to submit **Expressions of Interest (EOIs)** for product evaluation. The first Invitation to EOI for products for HIV/AIDS-related care and treatment was published in 2000 and the 9<sup>th</sup> Invitation was published in August 2009.

### **Article 1. Procedure for this Invitation to EOI**

The current Invitation is published in accordance with the *Procedure for prequalification of pharmaceutical products*, adopted in 2001 by the 37<sup>th</sup> WHO Expert Committee on Specifications for Pharmaceutical Preparations, and amended subsequently as part of the 43<sup>rd</sup> report of the Committee, published as [No. 953 of the WHO Technical Report Series](#) in 2009.

Assessment of product(s) submitted under this Invitation will include evaluation of :

- product dossiers, which must include product data and information as specified in the [guidelines for submission](#)
- manufacturing sites, which must adhere to [good manufacturing practices](#) (GMP)
- clinical sites (if applicable), which must adhere to [good clinical practices](#) (GCP).

If evaluation demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, it will be included in the [list](#) of medicinal products that are considered to be acceptable for procurement by UN organizations and others.

### **Article 2. Medicinal products included on the 10<sup>th</sup> Invitation**

The ultimate aim of this 10<sup>th</sup> Invitation is to increase the range of selected products and sources available in relation to treatment for HIV/AIDS. The medicines listed in the 10<sup>th</sup> Invitation have been identified by WHO Department of HIV/AIDS as vital to effective treatment for people living with HIV/AIDS. These products are included either in the [WHO Model List of Essential Medicines](#) and/or in the [WHO treatment guidelines relating to antiretroviral therapy for HIV infection in adults and adolescents](#), and [WHO treatment guidelines relating to antiretroviral therapy for HIV infection in infants and children](#).

Products included in the WHO Model List of Essential Medicines are those which satisfy the priority health care needs of a population. They are selected on the basis of disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness.

Products included in WHO treatment guidelines are selected on the basis of an assessment of the quality of evidence for benefits, harms, costs, and appropriateness for use in a variety of situations, taking into account needs of special populations, and the values and preferences of the groups (professional and patient) using them.

Interested manufacturers are encouraged to submit documentation for recommended dosage forms and strengths, as specified below, of medicinal products in the following categories. Appropriate solid dosage formulations should be scored for pediatric use purposes and relevant evidence should be provided to support equal distribution of active ingredients in the scored products, especially in case of fixed-dose combination products.

## 1. Antiretrovirals as single-ingredient formulations for use in adults and adolescents:

### 1.1. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

- Abacavir, tablet 300 mg; 600 mg
- Didanosine, capsule (enteric-coated) 200 mg; 250 mg; 400 mg,
- Emtricitabine, capsule 200 mg
- Lamivudine, tablet 150 mg; 300 mg
- Stavudine, capsule 30 mg
- Tenofovir disoproxil fumarate, tablet 300 mg
- Zidovudine, tablet 300 mg, capsule 250 mg

### 1.2. Non-Nucleoside Reverse Transcriptase Inhibitors

- Efavirenz, tablet 200 mg; 600 mg
- Nevirapine, tablet 200 mg
- Etravirine, tablet 100 mg

### 1.3. Protease Inhibitors

- Atazanavir, capsule 150 mg; 300 mg
- Ritonavir, capsule 100 mg, tablet (heat-stable) 100 mg
- Darunavir, tablet 300; 600 mg

### 1.4. Integrase Inhibitors

- Raltegravir, tablet 400 mg

## 2. Antiretrovirals as single-ingredient formulations for use in children:

### 2.1. Solid dosage formulations of :

- Abacavir, scored tablet 60 mg
- Didanosine, capsule (enteric-coated) 125 mg; 200 mg; 250 mg
- Didanosine, tablet, buffered or chewable 25 mg; 50 mg
- Darunavir, scored tablets 150 mg
- Efavirenz, scored tablet 100 mg; 200 mg
- Etravirine, tablet 25 mg
- Lamivudine, scored tablet 30 mg
- Nevirapine, scored tablet 20 mg; 50 mg; 100 mg
- Ritonavir, tablet (heat-stable) 25 mg
- Zidovudine, scored tablet 60 mg

## 2.2. Solutions or dissolvable formulations of:

- Abacavir, oral liquid 100 mg/5ml
- Emtricitabine, oral liquid 50 mg/5ml
- Lamivudine, oral liquid 50 mg/5ml
- Nevirapine, oral liquid 50 mg/5ml; sachet/granules 6 mg
- Zidovudine, oral liquid 50 mg/5ml; sachet/granules 12 mg
- Lopinavir + Ritonavir, sachet/granules (heat stable) 40 mg + 10 mg

## 3. Anti-retrovirals as fixed-dose combinations (FDC) for adults and adolescents:

### 3.1. Reverse Transcriptase Inhibitors:

- Lamivudine + Zidovudine, tablet 150 mg + 300 mg; tablet 150 mg + 250 mg
- Lamivudine + Zidovudine + Abacavir, tablet 150 + 300 mg + 300 mg,

### 3.2. Reverse Transcriptase Inhibitors plus Non-nucleoside Reverse Transcriptase Inhibitors:

- Lamivudine + Zidovudine + Nevirapine, tablet 150 mg + 300 mg + 200 mg, tablet 150 mg + 250 mg + 200 mg
- Tenofovir + Emtricitabine, tablet 300 mg + 200 mg
- Tenofovir + Lamivudine, tablet 300 mg + 300 mg
- Tenofovir + Efavirenz + Emtricitabine, tablet 300 mg + 600 mg + 200 mg
- Tenofovir + Efavirenz + Lamivudine, tablet 300 mg + 600 mg + 300 mg

### 3.3. Protease Inhibitors:

- Atazanavir + Ritonavir, tablet (heat stable) 150 mg + 50 mg; 300 mg + 100 mg
- Lopinavir + Ritonavir, tablet (heat-stable) 200 mg + 50 mg

## 4. Anti-retrovirals as co-packaged formulations for adults and adolescents:

### 4.1. Reverse Transcriptase Inhibitors plus Non-nucleoside Reverse Transcriptase Inhibitors:

- FDC tablet of tenofovir + lamivudine, 300 mg + 300 mg co-packaged with 2 single tablets of Nevirapine 200 mg
- FDC tablets of Tenofovir + Emtricitabine, 300 mg + 200 mg co-packaged with 2 single tablets of Nevirapine 200 mg

### 4.2. Reverse Transcriptase Inhibitors plus Protease Inhibitors:

- FDC tablets of Tenofovir + Lamivudine, 300 mg + 300 mg co-packaged with 1 FDC tablet of Atazanavir + Ritonavir (heat stable) 300 mg + 100 mg
- FDC tablets of Tenofovir + Emtricitabine, 300 mg + 200 mg co-packaged with 1 FDC tablet of Atazanavir + Ritonavir (heat stable) 300 mg + 100 mg
- FDC tablets of Tenofovir + Lamivudine, 300 mg + 300 mg co-packaged with 1 single tablet of Atazanavir 300 mg and 1 single tablet of Ritonavir + 100 mg (heat stable)
- FDC tablets of Tenofovir + Emtricitabine, 300 mg + 200 mg co-packaged with 1 single tablet of Atazanavir 300 mg and 1 single tablet of Ritonavir + 100 mg (heat stable)

## 5. Anti-retrovirals as fixed-dose combinations (FDC) for paediatric use:

### 5.1. Reverse Transcriptase Inhibitors:

- Lamivudine + Abacavir, tablet 30 mg + 60 mg
- Lamivudine + Zidovudine, tablet 30 mg + 60 mg
- Lamivudine + Abacavir + Nevirapine, tablet 30 mg + 60 mg + 50 mg
- Lamivudine + Stavudine + Nevirapine, tablet 30 mg + 6 mg + 50 mg
- Lamivudine + Zidovudine + Abacavir, tablet 30 mg + 60 mg + 60 mg
- Lamivudine + Zidovudine + Nevirapine, tablet 30 mg + 60 mg + 50 mg

### 5.2. Protease Inhibitors:

- Lopinavir + Ritonavir, tablet (heat-stable) 100 mg + 25 mg

## 6. Medicines to treat HIV/AIDS related conditions:

### 6.1. Antiviral agents:

- Acyclovir, tablets 200 mg, 400 mg, injecting vials 250 mg
- Gancyclovir, injecting vials 500 mg

### 6.2. Antibacterial agents:

- Amoxicillin + Clavulanic Acid, 250 mg + 62.5 mg (scored,) tablets 500mg + 125mg
- Azithromycin, tablets 250 mg, 500 mg
- Ceftriaxone, injecting vials 1 g
- Ciprofloxacin, tablets 250 mg, 500 mg
- Sulfadiazine, tablets 500 mg
- Sulfamethoxazole + Trimethoprim, 400 mg+ 80 mg (scored), 800 mg + 160 mg
- Sulfamethoxazole + Trimethoprim + Isoniazid + Pyridoxine, tablets 800mg + 160 mg + 300 mg + 25 mg

### 6.3. Antiprotozoal, antifungal and antimycobacterial agents:

- Amphotericin B , injecting vials 50 mg (deoxycholate)
- Clarithromycin, tablets 250 mg, 500 mg,
- Clindamycin, injecting vials 150 mg/ml, capsules 150 mg, 300 mg
- Dapsone , tablets 25 mg, 50 mg, 100 mg
- Flucytosine capsules 250 mg, injecting vials 10 mg/ml
- Fluconazole, capsules 50 mg, 200 mg , injecting vials 2mg/ml
- Folinic acid , tablets 15 mg
- Itraconazole , capsules 100 mg, 200 mg,
- Pentamidine , injecting vials 300 mg
- Pyrimethamine , tablets 25 mg
- Rifabutin , capsules 150 mg

### 6.4. Palliative care drugs:

- Amitriptyline, tablets 10 mg, 25 mg
- Chlorphenamine, tablet 4 mg; oral solution 2mg/5ml;
- Codeine, tablets 30 mg
- Cyclizine, tablets 50 mg; injecting vials 50 mg/ml
- Dexametasone, tablets 2 mg, injecting vials 4 mg/ml
- Diazepam, tablets 2, 5 mg (scored); injection vials 5 mg/ml

- Docusate, capsules 100 mg, oral solution 10 mg/ml
- Fluoxetine, tablets 20 mg
- Hyoscine hypobromide; tablets 10 mg, transdermal patches 1 mg
- Ibuprofen, tablets 200 mg, 400 mg, 600 mg
- Loperamide ,injecting vials 1 mg/ml ; 5mg/ml; oral solution 2 mg/ml
- Morphine, tablets 10 mg (immediate release), tablets 10 mg, 30 mg, 60 mg (controlled release), oral solution 10 mg/5 ml, granules 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
- Ondansetron, tablets 4mg, 8 mg, 24 mg; injecting vials 2mg/ml
- Prednisolone, tablets 5mg, 25 mg
- Senna, tablets 75 mg, oral solution 1.5 mg/ml

#### 6.5. Opioid substitution therapy used in drug dependence programmes:

- Buprenorphine, sublingual tablets 2mg,8 mg
- Methadone, concentrate for oral solution 5mg/ml, 10mg/ml ( hydrochloride); oral solution 5mg/5 ml, 10 mg/5ml

### **Article 3. How to submit an Expression of Interest**

In order to submit an expression of interest for product evaluation, the manufacturer must send the requested documentation, arranged according to the information provided on the WHO Prequalification of Medicines Programme web site at [www.who.int/prequal/](http://www.who.int/prequal/) section "Information for Applicants".

### **Article 4. Quality assessment procedure following submission of an expression of interest by a manufacturer**

The quality assessment is undertaken to evaluate whether the pharmaceutical product being evaluated meets the requirements recommended by WHO, and is manufactured in compliance with good manufacturing practices (GMP).

The procedure established by WHO for quality assessment incorporates:

- general understanding of the production and quality control activities of the manufacturer;
- assessment of product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- assessment of the manufacturing site's adherence to GMP, and its consistency in production and quality control of starting materials, with specific emphasis on active pharmaceutical ingredients, and finished product;
- assessment of clinical testing units or organizations (i.e. parties performing one or more clinical trials with the product) for compliance with good clinical practices and good laboratory practices, as appropriate;
- random sampling and testing of medicines supplied.

Previous evaluation conducted by the relevant National Drug Regulatory Authority (NDRA) may be taken into account during the evaluation conducted by WHO, provided that NDRA has expertise in the product area.

Once WHO is satisfied that quality assessment has been completed for the manufacturer of the relevant starting materials, the finished pharmaceutical product, and the clinical testing units, and that the product meets WHO recommended standards, the product (as produced at the specified manufacturing site) is added to the [WHO List of Prequalified Products](#).

## **Article 5. References and further information**

For further information on the WHO Prequalification of Medicines Programme, please visit the Programme's web-site at: [www.who.int/prequal/](http://www.who.int/prequal/).

For further information on WHO treatment guidelines, please consult:

1. WHO guidelines on "Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for public health approach", WHO, Geneva 2006; available at: <http://www.who.int/entity/hiv/pub/guidelines/artadultguidelines.pdf>
2. WHO guidelines on "Antiretroviral therapy for HIV infection in infants and children: recommendations for public health approach", WHO, Geneva 2006 available at: <http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf>
3. Report of meetings on paediatric ARV medicines; available at: <http://www.who.int/hiv/events/paediatricmeetingreport.pdf>