

## Recommended comparator products: Medicines for HIV/AIDS and related diseases

Comparator products should be purchased from a well-regulated market with stringent regulatory authority<sup>1</sup>

| Invited medicinal products<br>(refer to EOI for more information<br>e.g., requirements for scoring)  | Recommended comparator<br>product<br>(Strength, Marketing authorization<br>holder)   |
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| <b><i>Antiretrovirals as single-ingredient formulations</i></b>  |  |
| Abacavir, 60 mg, 300 mg and 600 mg tablet  | Ziagen (300 mg tablet, 20 mg/ml oral solution, GlaxoSmithKline)  |
| Atazanavir, 150 mg and 300 mg capsule (not invited; to be used in fixed dose combinations)   | Reyataz (150 mg and 300 mg capsule, Bristol- Myers Squibb)   |
| Cabotegravir, 600mg/3ml suspension for i.m. injection  | Apretude or Vocabria (600mg/3ml suspension for i.m. injection, ViiV Healthcare Co.)  |
| Cabotegravir, extended-release suspension for i.m. injection, 600mg/3ml (200mg/ml) + Rilpivirine, extended release suspension for i.m. injection, 900mg/3ml (300mg/ml) | Cabenuva (co-package 600 mg/3 ml (200 mg/ml) cabotegravir suspension + 900 mg/3 ml (300 mg/ml) rilpivirine suspension, for i.m. injection, ViiV Healthcare, US <sup>2</sup> )<br><br>Vocabria (600mg/3ml suspension for i.m. injection, ViiV Healthcare Co.) + Rekambys (900mg/3ml suspension for i.m. injection, Janssen-Cilag International) |
| Cabotegravir, 30 mg tablet   | Apretude or Vocabria (30 mg tablet, ViiV Healthcare Co.)   |
| Darunavir, 400 mg, 600 mg and 800 mg tablet  | Prezista (400 mg, 600 mg and 800 mg tablet, Janssen-Cilag/Tibotec)   |
| Dapivirine, silicone matrix vaginal ring, 25 mg  | Dapivirine Vaginal Ring 25 mg (International Partnership for Microbicides Belgium AISBL)   |
| Dolutegravir, 50 mg tablet<br><br>Dolutegravir (dispersible), 5 and 10 mg  | Tivicay (50 mg tablet, ViiV Healthcare Co.)<br><br>Tivicay PD (5 mg dispersible tablet, Viiv Healthcare Co.)   |
| Efavirenz, 600 mg tablet   | Sustiva (200 capsule, 600 mg tablet, Bristol Myers Squibb)<br>Stocrin (200 mg capsule, 200 mg and 600 mg tablet, 30 mg/ml oral solution, Merck Sharpe Dohme)   |

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| Emtricitabine ( <u>not invited</u> ; to be used in fixed dose combinations)              | Emtriva (200 mg capsule, Gilead Sciences Int. Inc)  |
| Etravirine, 100 mg and 200 mg tablet   | Intelence (100 mg and 200 mg tablet, Janssen-Cilag)   |
| Lamivudine, 150 mg tablet, 10 mg/ml oral liquid  | Epivir (150 mg, 10 mg/ml oral solution, GlaxoSmithKline)  |
| Lenacapavir, 463.5 mg/1.5 ml solution for s.c. injection                                 | Sunlenca (464 mg solution for injection, Gilead Sciences Inc.)                                    |
| Lenacapavir, 300 mg tablet   | Sunlenca (300 mg tablet, Gilead Sciences Inc.)  |
| Nevirapine, 10 mg/ml oral liquid   | Viramune (10 mg/ml oral suspension, Boehringer Ingelheim)   |
| Ritonavir, 25 mg (heat stable) tablet/pellets, 100 mg (heat stable) tablet               | Norvir (100 mg (heat stable) tablet, AbbVie Ltd)  |
| Tenofovir alafenamide 25 mg tablet (not invited; can be used in fixed dose combinations) | Vemlidy (25 mg tablet, Gilead Sciences Int. Inc)  |
| Tenofovir disoproxil fumarate, 300 mg tablet   | Viread (300 mg tablet, Gilead Sciences Int. Inc)  |
| Zidovudine 300 mg tablet, 250 mg capsule, 10 mg/ml oral liquid                           | Retrovir (300 mg tablet, 250 mg capsule, 10 mg/ml syrup, ViiV Healthcare)                         |
| <b>Fixed-dose combination products of antiretrovirals</b>                                |   |
| Abacavir/Dolutegravir/Lamivudine, 600 mg/50 mg/300 mg tablet                             | Triumeq (600 mg/50 mg/300 mg tablet, ViiV Healthcare)   |
| Abacavir/Dolutegravir/Lamivudine, 60 mg/5 mg/30 mg dispersible tablet                    | Triumeq PD (60 mg/5 mg/30 mg dispersible tablet, ViiV Healthcare)                                 |
| Abacavir/Lamivudine, 120 mg/60 mg and 600 mg/300 mg tablet                               | Kivexa (600 mg/300 mg tablet, GlaxoSmithKline)<br>Epzicom (600 mg/300 mg tablet, GlaxoSmithKline) |
| Efavirenz/Lamivudine/Tenofovir disoproxil fumarate, 400 mg/300 mg/300 mg tablet          | Symfi Lo (400 mg/300 mg/300 mg tablet, Mylan Pharmaceuticals Inc., US <sup>2</sup> )              |
| Emtricitabine/Tenofovir alafenamide, 200 mg/25 mg and 200 mg/10 mg tablet                | Descovy (200 mg/25 mg and 200 mg/10 mg tablet, Gilead Sciences Int. Inc)                          |

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| Emtricitabine/Tenofovir disoproxil fumarate, 200 mg/300 mg tablet  | Truvada (200 mg/300 mg tablet, Gilead Sciences Int. Inc)   |
| Lamivudine/Dolutegravir, 300 mg/50 mg tablet   | Dovato (50 mg dolutegravir/300 mg lamivudine tablet, ViiV Healthcare)  |
| Lamivudine/Tenofovir disoproxil fumarate, 300 mg/300 mg tablet   | CIMDUO (300 mg/300 mg tablet, Mylan Laboratories, USA <sup>2</sup> )   |
| Lamivudine/Zidovudine, 30 mg/60 mg and 150 mg/300 mg tablet  | Combivir (150 mg/300 mg tablet, GlaxoSmithKline)   |
| Lopinavir/Ritonavir, 100 mg/25 mg and 200 mg/50 mg (heat stable) tablet, 40 mg/10 mg (heat stable) granules or mini-tablets or pellets | Kaletra (100 mg/25 mg and 200 mg/50 mg tablet, 80 mg/20 mg oral solution, AbbVie Inc.)   |
| <b>Medicines to treat HIV/AIDS related conditions</b>  |  |
| Amphotericin B, 50 mg injection as deoxycholate, 50 mg liposomal injection   | Fungizone (50 mg/vial, Bristol-Myers Squibb)<br>Amphotericin B 50 mg/vial (X Gen Pharmaceuticals Inc., US <sup>2</sup> )<br>Ambisome (50 mg/vial, Gilead Sciences Int. Ltd.)<br>Ambisome (50 mg/vial, Astellas Pharma US Inc., US <sup>2</sup> ) |
| Benzathine Benzylpenicillin, 2.4 million units/4ml, 1.2 million units/2ml and 600000 units/1ml, powder for i.m. injection              | Bicillin L-A (2.4 million units/4ml, 1.2 million units/2ml and 600000 units/1ml suspension for i.m. injection, Pfizer/King Pharmaceuticals LLC)  |
| Clindamycin, 150 mg and 300 mg capsule, 150 mg/ml injection  | Dalacin C (250 mg and 300 mg capsule, 150 mg/ml injection, Pfizer)<br>Cleocin (150 mg and 300 mg capsule, 150 mg/ml injection, Pharmacia and UpJohn, US <sup>2</sup> )   |
| Fluconazole, 50 mg and 200 mg capsule, 2 mg/ml injection   | Diflucan (50 mg and 200 mg tablet/capsule, 2 mg/ml injection, Pfizer)  |
| Flucytosine, 250 mg capsule, 500 mg tablet, 10 mg/ml injection   | Ancabon (250 mg and 500 mg capsule, Valeant Pharmaceuticals Int., US <sup>2</sup> )<br>Ancotil (500 mg tablet, 10 mg/ml i.v. solution, Meda Pharma)  |
| Ganciclovir, 500 mg injection  | Cymevene (500 mg injection, Roche)<br>Cytovene (500 mg injection, Roche)   |
| Pyrimethamine, 25 mg tablet  | Daraprim (25 mg tablet, GlaxoSmithKline)<br>Daraprim (25 mg tablet, Turing Pharmaceuticals LLC., US <sup>2</sup> )   |

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| Sulfadiazine, 500 mg tablet   | Sulfadiazine 500 mg tablet (Sandoz Inc., US <sup>2</sup> )  |
| Sulphamethoxazole/Trimethoprim, 400 mg/80 mg and 800 mg/160 mg tablet | Septrin (400 mg/80 mg and 800 mg/160 mg tablet, Aspen)<br>Bactrim (400 mg/80 mg and 800 mg/160 mg tablet, Roche)<br>Bactrim (400 mg/80 mg and 800 mg/160 mg tablet, Sun Pharmaceutical Industries Inc., US <sup>2</sup> )<br>Cotrim (400 mg/80 mg and 800 mg/160 mg tablet, Ratiopharm) |
| Valganciclovir, 450 mg tablet   | Valcyte (450 mg tablet, Roche)<br>Valcyte (450 mg tablet, Hoffman-LaRoche, US <sup>2</sup> )  |

1 A regulatory authority that is:

- a) a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or
- b) an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or
- c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.

2 The recommended comparator products are approved by US FDA; the comparator product should be obtained from the US market.

### **Obtaining Comparator**

Comparator products should be purchased from a well-regulated market with stringent regulatory authority. If the recommended comparator cannot be located for purchase from the market of one of the identified countries, the applicant should consult with WHO regarding the sourcing of an acceptable comparator product.

### **Information Requirements**

Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence. Further, in order to prove the origin of the comparator product the applicant must present all of the following documents:

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.
2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive or equivalent responsible for the application to the Prequalification Programme.

### **Dose Equivalence**

In case the invited product has a different strength compared to the available acceptable comparator product, it is not always necessary to carry out a bioequivalence study at the same dose level; if the active substance shows linear pharmacokinetics, extrapolation between similar doses may be applied by dose normalisation.

### **Fixed-dose Combination Products**

The bioequivalence of fixed-dose combination (FDC) product should be established following the same general principles. The submitted FDC product should be compared with the respective innovator FDC product as listed above. In cases where a FDC comparator product is not listed above, individual component products administered in loose combination should be used as a comparator. The principles of dose normalization as mentioned above are applicable.

### **Suitability of a comparator product for BCS-based biowaiver applications**

Recommendation of an API for BCS-based biowaivers is made purely on the solubility, permeability, safety and related properties of the API (Class 1 or Class 3) – see the Biowaiver guidance documents on the WHO Prequalification website. It does not imply that the recommended comparator product(s) will be rapidly dissolving in case of Class 1 APIs (or very rapidly dissolving in case of Class 3 API), which is a requirement for BCS based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the Prequalification website is indeed suitable for a BCS based-biowaiver application before product development.

Note that rapidly dissolving (or very rapidly dissolving) properties of a product are not required for in vivo bioequivalence studies. Thus, though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for in vivo bioequivalence studies.