# Recommended Comparator Products: Reproductive Health Medicines

**Comparator products should be purchased from a well regulated market with stringent regulatory authority i.e., from countries participating in the International Conference on Harmonization (ICH).[1]**

| Invited medicinal products | Recommended comparator product (strength, manufacturer) |
|---|---|
| ***Oral hormonal contraceptives*** | |
| Desogestrel 75 µg tablet | Cerazette (75 µg tablet, MSD) |
| Ethinyl estradiol + desogestrel 30 µg + 150 µg tablet | Marvelon (Organon)<br>Varnoline (Organon)<br>Ortho-Cept (Janssen Pharms, US)Error! Bookmark not defined. |
| Ethinyl estradiol + levonorgestrel 30 µg + 150 µg tablet | Microgynon 30 (Schering AG)<br>Levora 0.15/30-28(Watson Labs, US)Error! Bookmark not defined. |
| Levonorgestrel 30 µg tablet | Microlut (levonorgestrel 30 µg tablet, Schering AG) |
| Levonorgestrel 750 µg tablet (pack of two) | Postinor-2 (two tablets each containing 750 µg levonorgestrel, Gedeon Richter)<br><br>NorLevo (two tablets each containing 750 µg levonorgestrel, Laboratoire HRA Pharma)<br><br>Plan B (two tablets each containing 750 µg levonorgestrel, Teva Branded Pharm, US) Error! Bookmark not defined. |
| Levonorgestrel 1.5 mg tablet (pack of one) | Postinor-1, Levonelle<br>(levonorgestrel 1.5 mg tablet, Gedeon Richter/Bayer)<br><br>NorLevo (levonorgestrel 1.5 mg tablet, Laboratoire HRA Pharma)<br><br>Plan B One-Step<br>(levonorgestrel 1.5 mg tablet, Teva Branded Pharm, US)Error! Bookmark not defined. |
| Norethisterone 350 µg tablet | Micronor (Janssen-Cilag) |
| Norgestrel 75 µg tablet | Neogest (Schering) |
| Ulipristal 30 mg tablet | Ella (30 mg tablet, LAB HRA Pharma, US)Error! Bookmark not defined.<br>Ella (30 mg tablet, HRA Pharma) |

[1] Countries officially participating in ICH are the ICH members European Union, Japan and USA; and the ICH observers Canada and EFTA as represented by Switzerland. Other countries associated with ICH (through legally binding mutual recognition agreements) include Australia, Norway, Iceland and Liechtenstein.

| Injectable hormonal contraceptives | |
|---|---|
| Medroxyprogesterone acetate (DMPA), depot injection (subcutaneous) 104 mg/0.65 ml | Depo-SubQ Provera 104 (Pharmacia and UpJohn, US)[2] |
| Medroxyprogesterone acetate (DMPA), depot injection 150 mg/ml | Depo-Provera (medroxyprogesterone acetate, depot inj 150 mg/ml, Pharmacia/Pfizer) |
| Medroxyprogesterone acetate (DMPA) + estradiol cypionate, injection 25 mg + 5 mg | Cyclofemina (medroxyprogesterone acetate 25 mg + estradiol cypionate 5 mg inj, Millet Roux Ltd, Brazil)[3] |
| Norethisterone enanthate, injection 200 mg | Noristerat (200 mg/ml, solution for intramuscular injection, Bayer) |
| Norethisterone enanthate + estradiol valerate, injection 50 mg + 5 mg | Mesigyna (norethisterone enanthate + estradiol valerate, 1 ml injection 50 mg + 5, Bayer Schering Pharma)[3] |
| *Hormonal intra-uterine device* | |
| Levonorgestrel intra-uterine system (reservoir 52 mg) | Mirena (Bayer) |
| *Implantable contraceptives* | |
| Two rod levonorgestrel-releasing implant; each rod containing 75 mg of levonorgestrel | Jadelle (two-rod levonorgestrel implant, each rod containing 75 mg of levonorgestrel, Bayer Schering Pharma) |
| Etonogestrel, implant containing 68 mg of etonogestrel | Implanon (Organon) |

| Uterotonics | |
|---|---|
| Oxytocin, injection 10 IU | Syntocinon (oxytocin 10 IU/ml inj, Novartis)<br><br>Pitocin (oxytocin 10 IU/ml inj, PAR Sterile Products LLC)2<br>Oxytocin 10 IU/ml inj (Eurohealth International SARL or Fresenius KABI LLC, US)**Error! Bookmark not defined.** |
| Mifepristone 200 mg tablet | Mifegyne (mifepristone 200 mg tablet, Exelgyn SA)<br>Mifeprex (mifepristone 200 mg tablet, Danco Labs LLC, US)**Error! Bookmark not defined.** |
| Misoprostol 25 µg and 200 µg tablet | Cytotec (misoprostol 100 µg, 200 µg tablet, Searle/Pfizer)<br>Cytotec (misoprostol 200 µg tablet, Searle/Pfizer) |
| *Prevention and treatment of eclampsia* | |
| Magnesium sulphate, injection 500 mg/ml | Magnesium sulphate 500 mg/ml (solution for injection, 1g/2ml, 5g/10ml, Fresenius Kabi, US)**Error! Bookmark not defined.** |

## Obtaining comparator

Comparator products should be purchased from a well-regulated market with stringent regulatory authority i.e. from countries participating in ICH. If the recommended comparator cannot be located for purchase from the market of an ICH-associated country, the applicant should consult with WHO regarding the sourcing of an acceptable comparator product.

[2] The recommended comparator product is approved by US FDA; the comparator product should be obtained from the US.
[3] Not available in ICH (associated) countries; product should be obtained from Brazil.

## Information requirements

Within the submitted dossier, the country of origin of the comparator product should be reported together with the lot number and expiry date, as well as the results of the 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 WHO Prequalification Team: medicines (PQTm).

## Dose equivalence

In case the invited product has a different dose 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 normalization.

## 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 active pharmaceutical ingredient (API) for BCS-based biowaivers is made purely on the solubility, permeability, safety and related properties of the API (Class 1 or Class 3) — 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 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. Though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for in vivo bioequivalence studies.