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# Etonogestrel and ethinylestradiol vaginal delivery system 0.12 mg/0.015 mg/day product-specific bioequivalence guidance

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| **Draft Agreed by Pharmacokinetics Working Party (PKWP)** | February 2019 |
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| **Keywords** | ***Bioequivalence, etonogestrel, ethinylestradiol*** |



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# Etonogestrel and ethinylestradiol vaginal delivery system 0.12 mg/0.015 mg/day product-specific bioequivalence guidance

*Disclaimer:*

*This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.*

## Requirements for bioequivalence demonstration (PKWP)*

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| **Bioequivalence study design** | **Single dose** in healthy female volunteers. |
| | **Cross-over design**<br><br>**Additional study considerations:** The authorised duration of treatment is 3 weeks. The originator product information states that the product continues to be effective if it is used for an additional 4$^{th}$ week. The extended ring use (of up to 28 days) should therefore be considered. A bioequivalence study for 28 days is recommended.<br><br>Bioavailability of etonogestrel is influenced by the level of sex hormone-binding globulin. Ethinylestradiol induces sex hormone-binding globulin. This should be considered in design of the run-in period and wash-out period between treatments. |
| | **Strength:** 0.12 mg /0.015 mg/day as a vaginal delivery system containing etonogestrel and ethinylestradiol.<br><br>**Background:** Only one strength |

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| **Analyte** | ☒ **parent** ☐ **metabolite** ☐ **both** |
| | ☒ **plasma/serum** ☐ **blood** ☐ **urine** |
| | **Enantioselective analytical method:** ☐ **yes** ☒ **no** |
| **Bioequivalence assessment** | **Main pharmacokinetic variables:** $C_{max}$, $C_{\tau,ss=21\ days}$ (concentration at day 21), $AUC_{(0\text{-}21\ d)}$, $C_{\tau,ss=28\ days}$ (concentration at day 28) and $AUC_{(0\text{-}28\ d)}$.<br><br>**Additional parameters for temporary removal of the ring:** Temporary removal of the ring needs to be justified by in vitro data demonstrating that etonogestrel and ethinylestradiol levels, their release rate, and quality of the ring are not affected by temporary removal of the ring up to a maximum of 3 hours. The influence of light, temperature, microbiological contamination and washing of the ring should be taken into account. |
| | **90% confidence interval:** 80.00–125.00% |

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of $C_{max}$, $C_{\tau,ss}$. If high intra-individual variability ($CV_{intra}$ > 30%) is expected, the applicants might follow respective guideline recommendations.