EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2018
EMA/CHMP/291499/2018
Committee for Medicinal Products for Human Use (CHMP)

# Apixaban film-coated tablet 2.5 and 5 mg product-specific bioequivalence guidance

Draft

| | |
|---|---|
| **Draft Agreed by Pharmacokinetics Working Party (PKWP)** | April 2018 |
| **Adopted by CHMP for release for consultation** | 31 May 2018 |
| **Start of public consultation** | 27 June 2018 |
| **End of consultation (deadline for comments)** | 30 September 2018 |

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

| | |
|---|---|
| **Keywords** | ***Bioequivalence, generics, apixaban*** |

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# Apixaban film-coated tablet 2.5 and 5 mg 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)*

| | |
|---|---|
| **BCS Classification**** | **BCS Class:** ☐ **I** ☐ **III** ☐ **Neither of the two**<br>**Background:** Apixaban is a compound with incomplete absorption, but the available data on solubility does not allow its BCS classification. If the applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, apixaban could be classified as BCS class III drug and a BCS-based biowaiver could be applicable. |
| **Bioequivalence study design**<br>*in case a BCS biowaiver is not feasible or applied* | **single dose**<br>**cross-over** |
| | **healthy volunteers** |
| | ☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed** |
| | **Strength:** 5 mg |

| | |
|---|---|
| | **Background:** Apixaban shows linear pharmacokinetics in dose range 2.5 - 10 mg. If it can be demonstrated that apixaban is highly soluble, in principle any strength may be used. |
| | **Number of studies:** One single dose study with intact tablets.<br>An additional study may be required with crushed tablets, unless scientifically justified. |
| **Analyte** | ☒ **parent** ☐ **metabolite** ☐ **both** |
| | ☒ **plasma/serum** ☐ **blood** ☐ **urine** |
| | **Enantioselective analytical method:** ☐ **yes** ☒ **no** |
| **Bioequivalence assessment** | **Main pharmacokinetic variables:** $AUC_{0-t}$ and $C_{max}$ |
| | **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 $C_{max}$. If high intra-individual variability ($CV_{intra}$ > 30 %) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary (BCS Class I and III), the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. *in vitro* dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).