Pegylated liposomal doxorubicin hydrochloride concentrate for solution 2 mg/ml product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP) | April 2018
---|---
Adopted by CHMP for release for consultation | 31 May 2018
Start of public consultation | 5 July 2018
End of consultation (deadline for comments) | 30 September 2018
Agreed by Pharmacokinetics Working Party (PKWP) | October 2018
Adopted by CHMP | 13 December 2018
Date of coming into effect | 1 July 2019

Keywords

| Bioequivalence, generics, pegylated liposomal doxorubicin hydrochloride |

© European Medicines Agency, 2018. Reproduction is authorised provided the source is acknowledged.
Pegylated liposomal doxorubicin hydrochloride concentrate for solution 2 mg/ml 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)*

<table>
<thead>
<tr>
<th>Bioequivalence study design</th>
<th>Single dose study: Any dose (but no dose adjustments for toxicities during the study) in e.g. stable ovarian/breast cancer patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Background:</strong> Dose proportional pharmacokinetics.</td>
</tr>
<tr>
<td></td>
<td><strong>cross-over</strong></td>
</tr>
</tbody>
</table>
|                             | **Other critical aspects:** The single dose study may need to be conducted with standardized light meals 
                             | rather than in the fasting state due to patient’s needs.                                                                                  |
| Analyte                     | □ total drug □ encapsulated drug □ unencapsulated drug □ doxorubicinol (metabolite)                   |
|                             | **Other critical aspects:** Unencapsulated drug concentrations must be achieved by means of appropriate |
bioanalytical methods rather than by subtracting encapsulated from total drug.

<table>
<thead>
<tr>
<th>plasma/serum</th>
<th>blood</th>
<th>urine</th>
</tr>
</thead>
</table>

**Enantioselective analytical method:**  
- yes  
- no  

### Bioequivalence assessment

**Main pharmacokinetic variables:** $AUC_{0-\tau}$, $AUC_{0-\infty}$, $C_{\text{max}}$, partial AUCs (e.g. $AUC_{0-48h}$ and $AUC_{48-\text{tlast}}$)

**Background/justification:** $AUC_{0-\tau}$, $AUC_{0-\infty}$ and $C_{\text{max}}$ for encapsulated and unencapsulated drug. Partial AUCs for the encapsulated drug to ensure profile comparability.

**90% confidence interval acceptance limits:** 80.00 – 125.00%

### Additional information can be added if considered necessary

**To be noted:** Proving equivalent efficacy and safety of a liposomal formulation developed to be similar to an innovator product is considered a step-wise approach which in addition to the pharmacokinetic study also takes account of quality and non-clinical comparison, where appropriate.

* 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 $C_{\text{max}}$, $C_{\tau}$, ss and partial AUC. If high intra-individual variability ($CV_{\text{intra}} > 30\%$) is expected, the applicants might follow respective guideline recommendations.