Appendix A: Decision trees for the evaluation criteria 5 to 11

Decision tree 1: Mechanism of DDI

Mechanism of DDI

Are details stated in the PI?

Yes

Details on known mechanism stated

Yes

Details on postulated mechanism stated

Yes

Mechanism unknown or not fully understood stated

Yes

Relevant information is absent in PI

No
Decision tree 2: Dose of drugs co-administered in the DDI study

1. Dose of drugs co-administered in DDI study

2. Are details stated in the PI?
   - Yes
   - No

   If Yes:
   - Dose of which drug(s) in drug pair stated?
     - Both drugs in drug pair
       - Yes
     - One of the drugs in a drug pair
       - Partial
     - DDI was extrapolated from other DDI stated
       - NA
     - DDI can be avoided by staggering the administration of drugs stated
       - NA
     - Relevant information is absent in PI
       - No

   If No:
     - NA
     - NA
     - NA
     - No
Decision tree 3: Duration of drugs co-administered in the DDI study

1. Duration of drugs administered in DDI study
   - Yes
   - No
     - Are details stated in the PI?
       - Yes
         - Duration of which drug(s) in drug pair stated?
           - Both drugs in drug pair
             - Yes
           - One of the drugs in a drug pair
             - Partial
           - DDI was extrapolated from other DDI stated
             - NA
           - DDI can be avoided by staggering the administration of drugs stated
             - NA
         - Relevant information is absent in PI
           - No
       - No

a: Change in PK parameters should be reported quantitatively, for example as a percent or fold change.  

Decision tree 4: Effect of DDI on PK parameter

- **Changes in Pharmacokinetic parameter**
  - Are details stated in the PI?
    - Yes
      - Is quantitative figures reported? a
        - Yes
          - DDI based on case reports stated
        - Partial
          - DDI based on extrapolation from other DDI stated
      - No
        - NA
          - No clinically significant DDI stated
        - NA
          - Relevant information is absent

a: Change in PK parameters should be reported quantitatively, for example as a percent or fold change.  

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Variability of the DDI

Are details stated in the PI?

- Yes
  - DDI based on case reports stated
    - Yes
    - NA
  - DDI based on extrapolation from other DDI stated
    - NA
  - No clinically significant DDI stated
    - NA
  - DDI study conducted but relevant information not included in PI
    - No

- No

a: Variability of DDI is presented as geometric mean change of PK parameter and the 90% confidence interval around the geometric mean change.27
Decision tree 6: Dose adjustment recommendation

Dose adjustment recommendation

Are details stated in the PI?

Yes

Are specific dose adjustment recommendations provided?

Yes

Is this information necessary?

Yes

Yes

Yesa

Partiob

NAc

Yes but unavailable

No

No

No
d

NAe

No

Unclear

Is dose adjustment required?

No

NAe

a: It is stated in the PI that appropriate dose to be adjusted to is not established yet.
b: Dose adjustment is suggested but no specific recommendations are provided.
c: It is stated in the PI that no dose adjustment is required for the drug pair.
d: The lack of description in the package insert renders it difficult to judge if any dose adjustment is required.
e: It is stated in the PI that co-administration of drug pair is contraindicated OR DDI is based on case report OR DDI is based on extrapolation from other DDI OR DDI is not clinically significant OR clinical significance of DDI findings is unclear.
Decision tree 7: Monitoring recommendation

- Monitoring recommendation
- Are details stated in the PI?
  - Yes
  - Are specific monitoring recommendations provided?
    - Yes
    - Yes
    - No
    - Partial
  - No
  - Unclear
- No
  - Is monitoring required?
    - No
    - No
    - No
    - NA
    - Unclear

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a: The lack of description in the package insert renders it difficult to judge if monitoring is required.
b: It is stated in the PI that co-administration of drug pair is contraindicated OR co-administration of drug pair does not require any dose adjustment OR DDI is not clinically significant OR clinical significance of DDI findings is unclear.