RESPONSE DOCUMENT

INITIAL QUALIFICATION PROCEDURE –
SECOND REQUEST FOR ADDITIONAL INFORMATION –

FLUVOXAMINE SUMMARY

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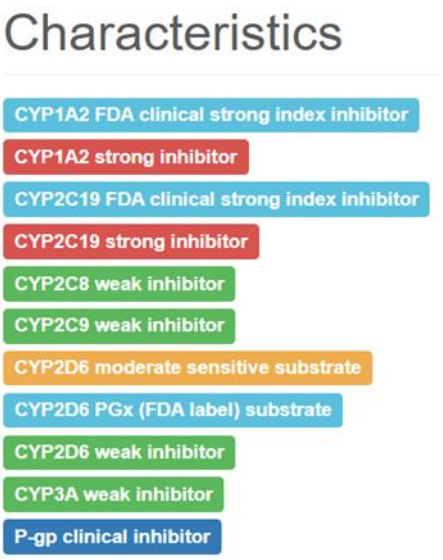
General comments from Certara: We note that the EMA have requested additional information for the fluvoxamine summary and made some more general comments/requests that relate to all compound file summaries. Below, we have replied to the fluvoxamine related comments but are currently addressing all of the others. In the accompanying compound file summary for fluvoxamine, we have indciated the changes in yellow.

We appreciate the updates performed by Certara, in particular adding references for some of the input parameters as well as highlighting the clinical DDI study used for parameter optimisation are useful.

Some comments for additional improvement are found below:

1. *Clarification of DDI properties not included in the model*

A summary of the general DDI characteristics of fluvoxamine can be retrieved from the Washington database, see below. We suggest that each compound file document should clearly state which of the known DDI characteristics were included and which were <u>not</u> incorporated in the compound file.



<u>RESPONSE:</u> The above has now been integrated at the beginning of the compoud file summary.

The lack of information on Pgp is now mentioned in a short section in the end of the fluvoxamine compound file document where it has been pointed out what was not considered in the model, but it could be written a bit more clearly (e.g. to mention P-gp inhibition by fluvoxamine as perpetrator instead of a general statement about transporters).

<u>RESPONSE:</u> This has now been explicitly stated that Pgp inhibition was not conisdered in the model. In addition, it has been stated that none of the subtrates used in the DDI have been

categorised as P-gp inhibitors according to the UOW database (now Certara Drug Interaction Solutions database).

In addition, it would be relevant to mention potential drawbacks of individual substrate ("victim") compound files which were used in combination with fluvoxamine as perpetrator. E.g. Has Certara verified that none of the "victim" drugs in the tables are also known as P-gp substrates and/or CYP2C8 substrates (i.e., this would then not be covered by the current DDI fluvoxamine compound file)? If no victims that may be influenced by Pgp or CYP2C8 inhibition are present in the tables, this may be spelled out e.g. in the table heading or footnote. If, on the other hand, there are victim drugs in the tables (that are not part of this qualification and) that may have additional DDI mechanisms, this needs to be highlighted in the tables.

RESPONSE: We have now clarified that none of the substrates used for assessment of DDI are considered to be CYP2C8 or P-gp substrates according to the UOW (now Certara Drug Interaction Solution Database). The text shown below appears in the compound file summary.

• Inhibition of CYP2C8.
It should be noted that none of the substrates evaluated for DDI potential in this compound summary are classified as a CYP2C8 substrate (Certara Dug interaction solutions database).

• Inhibition of P-gp.
It should be noted that none of the substrates evaluated for DDI potential in this compound summary are classified as a P-gp substrate (Certara Dug interaction solutions database).

2. *Further clarification of origin and adjustment of some of the parameters needed*

   a) In the table with Ki parameters for most CYP enzymes it is written: "Original value derived from meta-analysis of in vitro HLM data. Value lowered ten-fold as ten-fold difference between in vitro and in vivo Ki for fluvoxamine reported (Yao et al., 2001)". This is a very important parameter adjustment, and some more details would be useful (are the details of this meta-analysis and adjustment fully clear from the publication?)

RESPONSE: As stated previously, for the non-CYP1A2 enzymes, meta-analyses of available *in vitro* Ki values were performed. In our table of input parameters, we have now indicated the source of in vitro data used in the meta- analysis of each Ki value.

The resultant Ki values were reduced by 10-fold; this scalar was derived in the clinical study by Yao et al. (2001) to account for the differential between the performance of *in vitro* and *in vivo* Ki values. The above is indicated in the text (see below) and Table 11. This study was not used to assess the performance of fluvoxamine for DDI studies involving CYP2C9, CYP2C19, CYP2D6 or CYP3A4 i.e. it is not part of the DDI qualification matrix for these enzymes (Tables, 3,4,5,6,7,8,9,10).

In the text under the heading Interaction, it is stated that "Based on a publication by Yao et al., 2001, it is reported that the "*fluvoxamine inhibition potency is about 10-fold greater in vivo than in vitro."* The latter statement is taken straight out of the publication – we have put this in *italics* to indicate this.

b) The following are further examples of parameters where there is no meaningful explanation or origin and where more details would be useful:

logP ("meta-analysis" without further explanation)
B/P ("Simcyp archive, consortium member data")
Qgut ("predicted" without further explanation)

RESPONSE: Where possible, we have clarified the source of data. Not all of the parameters have been published and some have been made available by Consortium members.