The full evidence and feasibility review for sertraline dosing in pregnancy can be found in the supplementary materials of this article. A summary for healthcare practitioners is outlined below in this document.

EXECUTIVE SUMMARY FOR HEALTHCARE PRACTITIONERS

Sertraline is a widely used antidepressant during pregnancy. The current dosing strategy for sertraline in nonpregnant adults follows a 'start low, go slow' approach, whereby a dose is titrated based on the effect on an individual patient's symptoms within a 25-200 mg range.

So far, no specific dose recommendation in pregnancy for sertraline has been issued. Changes in the distribution and metabolism of sertraline during pregnancy may justify an alteration of the standard dosing strategy followed in nonpregnant adults (see **Part 2** on the clinical and pharmacological arguments for investigating the dose of sertraline in pregnancy).

Part 3.1. of this document examines information on the use and safety of sertraline in pregnancy. **Part 3.2** summarizes the available knowledge on the pharmacokinetics of sertraline in nonpregnant adults. **Part 3.3.** then looks at the pharmacokinetics, dose-related efficacy and safety data of sertraline during pregnancy. The findings of **Part 3** can be summarized as follows:

- A large variation in the pharmacokinetics of sertraline (i.e. how sertraline is processed by the body, resulting in a given plasma concentration) is observed among nonpregnant individuals. This variation is most likely related to genetic variation in the multiple hepatic (CYP) enzymes responsible for metabolizing sertraline. This variation means that it is hard to define a therapeutic range (i.e. a concentration range for which the medication works with optimal safety and efficacy). There is no clear toxic threshold for sertraline (i.e. a dose or blood concentration at which it is known to cause harm) but toxicity occurs infrequently outside of pregnancy.
- It is likely that pregnancy-induced changes in maternal physiology result in an overall decrease in the maternal plasma concentration of sertraline, especially in the second and third trimesters, in comparison to pre-pregnancy levels. While the extent of this decrease is hard to quantify, it is likely to be moderate on average, with some variation across pregnant individuals.
- The latter decrease is likely to be for a large part caused by the combined effect of CYP enzyme induction (apart from CYP2C19) and a decrease in albumin concentration during pregnancy. The interindividual variability in maternal exposure to (i.e. the plasma concentration of) sertraline during pregnancy can most likely be attributed to genetic variation in CYP2C19.
- The latter information was obtained from a combination of small, moderate-quality pharmacokinetic studies (described in **Paragraph 3.3.1**) and a physiologically-based pharmacokinetic model in pregnancy (described in **Paragraph 3.3.2).**

- All in all, these pharmacokinetic data suggest that the dose of sertraline should not be reduced and may even have to be increased for certain pregnant women in the second or third trimesters of pregnancy depending on the clinical response to treatment over time.

- Our knowledge of the effect of pregnancy on the pharmacodynamics of sertraline (i.e. the mechanisms through which sertraline exerts its effects) is insufficient to inform a pregnancy-adjusted dose.

- While there is a paucity data on the fetal toxicity of sertraline in relationship to dose (none available for most fetal and neonatal outcomes), evidence of a dose relationship between the occurrence of poor neonatal adaptation syndrome (i.e. a combination of transient neurological symptoms resulting from sertraline withdrawal shortly after birth) and the use of doses of sertraline ≥ 100 mg in the third trimester of pregnancy was found. The latter dose-effect relationship may exist for other fetal or neonatal outcomes and may constitute a trade-off for dosage increase in the third trimester of pregnancy.

The latter information was used to issue the dose recommendation of sertraline in pregnancy outlined in **Part 1** of this document, which also includes questions to the Working Committee.

Part 4 examines the feasibility and acceptability of the proposed dose. In short,

- The level of confidence in the proposed dosing strategy appears sufficient. Despite variations in the pharmacokinetics of sertraline across individuals and the lack of a well-established maternal therapeutic range as a reference for dosing, a cautious approach was adopted for issuing a pregnancy-adjusted dose (i.e. use of a conservative reference range for identifying an optimal dose through modelling). Based on the chosen approach, some pregnant women may be underdosed but maternal overdosing appears unlikely. The risk of maternal overdosing also appears minimal given our recommendation to titrate the dose based on a pregnant individual's clinical response to sertraline. One area of uncertainty concerns fetal toxicity in relationship to dose, which is most likely to be a consideration for dosing in the third trimester of pregnancy given the association between third trimester exposure and at least one (transient) neonatal outcome.

- The recommended dose strategy appears feasible as it does not significantly depart from the dose recommendation in nonpregnant adults.

- The Working Committee deems the proposed dose acceptable taking into account the direct **maternal benefits** of an appropriately treated depression and/or anxiety disorder and the indirect **fetal benefits**, including a lower risk of adverse perinatal outcomes including prematurity, intrauterine growth restriction, and a reduced likelihood of maternal stress and potentially harmful maternal behaviors. While in theory, a higher dose of sertraline could be linked to an **increased risk of fetal harm**, the absolute incidence of permanent fetal defects associated with sertraline use is very low and the recommended dose remains with the standard range for which the latter data were obtained. Overall, in light of this positive risk-benefit ratio, the Working Committee finds the proposed dose to be advisable.

- Added value: while the proposed dose does not fundamentally deviate from the dose in nonpregnant adults, it is based on a more extensive review of the available evidence as well as on an explicit discussion of the fetal and maternal benefits and risks involved which may help create more certainty and uniformity in dosing practices in pregnancy.