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[redacted]

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Vigilance & Risk Management of Medicines Division
Medicines and Healthcare products Regulatory Agency (MHRA)
Market Towers
1 Nine Elms Lane
London SW8 5NQ
UNITED KINGDOM

Agence Française de Sécurité Sanitaire des Produits de Santé
Direction de l'Evaluation des Médicaments et des Produits Biologiques
143-147, boulevard Anatole
93200 SAINT DENIS
FRANCE

Attn: [redacted]

Prozac® (fluoxetine) 20 mg capsule (PL00006/0195), 20 mg/5 mL liquid (PL00006/0272), 20 mg dispersible tablets (NL 22298)

Follow-Up Measure (FUM): To assess the findings of juvenile toxicity studies conducted to investigate the effect of fluoxetine on neurohormonal sexual maturation and testicular pathogenesis in rodents

Response to List of Questions in Final Joint Assessment Report

Dear [redacted]

Following the extension of the indication of fluoxetine to include the treatment of a moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions, in children and adolescents aged 8 years and above, Lilly had a specific obligation to conduct three pharmaco-toxicological studies in juvenile rats, and a subsequent FUM:

> "*If the RMS considers that the results of the preclinical studies warrant label changes or further study, we agree to discussions with the RMS to assess what further measures would be valid, useful and achievable.*"

Two of the three final study reports (901143 and 901144) have been assessed, and a Final Joint Assessment Report was received on 14 October 2008. The third final study report (F3) was submitted on 29 August 2008 and is still under assessment. Please find attached Lilly's response to the list of questions requested in the current assessment report.

The assessment report recommended:

> "*Once data confirming an absence of a treatment related effect on FSH and LH levels has been provided, the MAH will be requested to submit a type II variation to update section 5.3 of the Prozac SmPC with the study findings in order to inform prescribers that the testicular pathology and delayed sexual maturation are not SSRI class effects mediated through an action on the hypothalamus.*"

Lilly does not believe that the results of studies 901143 and 901144 warrant any changes or additions to the information already provided in section 5.3 of the SmPC. The results of studies 901143 and 901144 confirm the presence of the previously identified testicular lesions and established that fluoxetine had no effect on the hypothalamic-pituitary-gonadal (HPG) axis in maturing rats. These data do not affect the benefit-risk assessment and therefore do not justify changes to section 5.3.

In accordance with the FUM, Lilly proposes that discussions relating to any potential update to section 5.3 do not take place until all three studies have been assessed. Moreover, the renewal procedure for Prozac has not yet completed and Lilly has already submitted another two type II variations in parallel (UK/H/0636/01,03/II/020 & FR/H/0242/01/II/016; UK/H/0636/01,03/II/021 & FR/H/0242/01/II/017), which impact the SmPC, and for which the timetables will start once the renewal has been finalised. Therefore, Lilly does not believe it is feasible to submit further SmPC changes at this time, and requests that, as per the commitment, label discussions do not occur until all three pharmaco-toxicological studies included in this FUM have been assessed.

If you require any additional information, please do not hesitate to contact me.

Yours faithfully,