15 December 2016
EMA/CHMP/620297/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on Levodopa/Carbidopa/Entacapone film-coated tablet 200 mg/50 mg/200 mg, 175 mg/43.75 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 100 mg/25 mg/200 mg, 75 mg/18.75 mg/200 mg and 50 mg/12.5 mg/200 mg product-specific bioequivalence guidance' (EMA/CHMP/805630/2016)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Pharma Desk Solutions Private Limited

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We feel that the design / approach proposed in the draft guidance with respect to bioequivalence study of Levodopa / Carbidopa/ Entacapone is appropriate, however we would like to bring to your notice some of the concerns. Based on our prior experience & data from available literature with the combination molecule, we have the following concerns : 1) More number of adverse events were reported (Vomiting, Nausea, Abdominal pain & Diarrhoea) in the Levodopa / Carbidopa/ Entacapone studies were especially seen with "Entacapone" since whereas the adverse events were not observed at equal frequency in the "Levodopa / Carbidopa" studies. 2) All the reported adverse events were occurred during the early hours of the study (i.e. during the attainment of Cmax concentrations) leading to withdrawal of subjects which seems to be as high as 50% of sample size. 3) High rate of withdrawal subjects will have huge impact on the study outcome. Considering the possibility of adverse events reported & keeping in view of the safety of subjects, we recommend to include the use of concomitant medication like "Anti-emetic" drugs in the product specific guidance to avoid the occurrence of adverse events to	The comments have been acknowledged. The adverse events are however foreseen in healthy volunteers with products containing three different active substances. The comment has been acknowledged. Experience from clinical studies have however not revealed significant difficulties. If anti-emetics are administered, the study design should be standardized and all subjects should be

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	healthy subjects & proper execution of study.	treated in the same way. It should be noticed that anti-emetic drugs may cause additional adverse events and interfere with the absorption of the studied active substances.