CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-415/S-003

CLINICAL PHARMACOLOGY BIOPHARMACEUTICS REVIEW

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-415 Submission Date: November 18, 1996

Generic Name, Strength(s), and Formulation: **Mirtazapine (Org 3770) 15 mg, 30 mg, and [redacted] Scored, Film-coated, Oval-Shaped, Immediate Release Tablet for Oral Administration.**

Brand Name: **REMERON™**

Sponsor: Organon Inc
West Orange, New Jersey

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Review of Supplement For a New 45 mg Tablet

REVIEW OF SUPPLEMENT FOR A NEW 45 mg TABLET

Remeron™ (mirtazapine) is a weakly basic tetracyclic compound belonging to the piperazinoazepine group of compounds. It was approved for the treatment of depression on June 14, 1996. The usual effective dosing range is 15-45 mg administered daily at bedtime. Currently, Remeron™ is available in the market as 15 mg and 30 mg film-coated, immediate release tablets for oral administration. The drug displays linear kinetics over the dosing range of 15-80 mg/day.

This submission introduces a new tablet strength (viz., 45 mg tablets) to improve patients' dosing convenience. From an OCPB standpoint, this submission contains a "waiver request", more formally, waiver of evidence of in vivo bioavailability - 21 CFR 320.22(d)(2) (Attachment A). This implies demonstrating evidence *in vitro* in lieu of *in vivo* data.

Discussion:

This consult comes to OCPB with the viewpoint that for marketing the new higher strength of 45 mg that a biostudy would not be necessary, and that *in vitro* comparative dissolution profiles to the already approved 15 mg and 30 mg tablets, would suffice.

As mentioned, a dose of 45 mg is currently the highest of the maintenance dose and therefore, 45 mg as a "dose" is not new. Further, the drug displays linear kinetics up to

80 mg/day. The bioavailability of 15 mg and 30 mg tablets was established in the original NDA submission. This *in vivo* information coupled with the fact that the new tablet strength (45 mg) is compositionally proportional to the existing 15 and 30 mg tablet strengths, would reasonably allow for approving the 45 mg tablet on the basis of comparative *in vitro* dissolution data. Details follow:

Attachment 1 shows the composition of the currently approved 15 mg and 30 mg tablet formulations as well as the new 45 mg tablet formulation. The three formulations are compositionally proportional.

The following dissolution methodology and specification were recommended for the currently approved mirtazapine 15 mg and 30 mg tablets (original NDA):

Apparatus:	USP Apparatus 2 (Paddle)
Paddle speed:	50 rpm
Medium:	900 mL of 0.1N HCL at 37±0.5 °C
Specification:	

Dissolution testing was performed for the new 45 mg tablet strength as well as the two currently approved 15 and 30 mg tablet strengths using USP Apparatus 2 at paddle speed of 50 rpm in 900 mL of 0.1N HCL.

Attachment 2 shows the individual (n=12 units/lot) as well as range and mean±%RSD dissolution data at 5, 10, 15, 20, 30, 45, and 60 minutes for the 15 mg (5 lots), 30 mg (4 lots), and 45 mg (3 lots) mirtazapine tablets (Tables 1-19 and Figures 1-3). The average percentage of mirtazapine from dissolution profiles of various lots is summarized in Table 20 and Figure 4.

Dissolution was fast; the mean % mirtazapine dissolved was greater than 90 % at 15 minutes from all lots for the three tablet strengths (Table 20, Attachment 2). It is also seen that *in vitro* dissolution profiles of the new 45 mg strength are comparable to those obtained for the lots of the other strengths (15 mg and 30 mg) (Figure 4, Attachment 2).

Variability: % RSD at 15 minutes (the sampling time in the specification) ranged from 2-6 %, and comparable variability was observed for the 45 mg tablet in relation to 15 mg and 30 mg tablets.

In conclusion, the submitted *in vitro* dissolution data showed that % mirtazapine dissolved from the new 45 mg tablet has very comparable profiles to the currently

approved strengths of 15 mg and 30 mg tablets, and that the 45 mg tablet can meet the specification o[illegible]

COMMENTS:

(To be sent to the firm)

(1) The new 45 mg tablet strength meets the recommended dissolution specification of [illegible] using USP Apparatus 2 at 50 rpm paddle speed in 900 mL of 0.1N HCL at 37±0.5 °C. Approval of this strength is granted based on the submitted dissolution data.

(2) The sponsor is requested to note that the same dissolution methodology and specification that were recommended for the current 15 mg and 30 mg tablets are also being extended to include the new 45 mg tablet strength:

Apparatus:	USP Apparatus 2 (Paddle)
Paddle speed:	50 rpm
Medium:	900 mL of 0.1N HCL at 37±0.5 °C
Specification:	[illegible]

RECOMMENDATION:

The new 45 mg tablet strength is acceptable based on the submitted dissolution data and no *in vivo* bioavailability study is necessary.

Please forward the above Recommendation and Comments 1 and 2 to the firm.

/S/

Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT initialed by R. Baweja, Ph.D. /S/

cc: NDA # 20-415 (Suppl.), HFD-120, HFD-860 (Ibrahim, Baweja, Malinowski), HFD-19 (FOI), and Drug files (Mira Millison, HFD-850, Woodmont II, 3rd floor).

TRADE SECRET PAGES

29 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.