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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-615

Pharmacology Review(s)

Clinical Pharmacology and Biopharmaceutics Review

NDA :	21-615
Sponsor:	J&JPRD
Compound:	REMINYL (galantamine hydrobromide)
Formulation	Modified release capsules
Submission Date:	29 December 2004
Submission Materials	Meeting Package
Sponsor Meeting Date	24 January 2005
Reviewer:	Christine E. Garnett

Background

Galantamine is a reversible, competitive acetylcholinesterase inhibitor. It also allosterically modulates nicotinic receptors so as to potentiate the receptor response to acetylcholine and elevates cortisol concentrations.

It is approved and marketed in the US as the hydrobromide salt as Reminyl® 4 mg/ml oral solution (N21-224) and as 4 mg, 8 mg, and 12 mg (base equivalent) oral tablets (N21-169) by JANSSEN PHARMA, for "the treatment of mild to moderate dementia of the Alzheimer's type.

The sponsor submitted a NDA for a modified-release formulation (8 mg, 12 mg, and 24 mg capsules) on 02/23/03 for the treatment of mild to moderate Alzheimer's disease. The Division responded to that application with a Not-Approvable action letter on 12/23/03. Subsequently, the sponsor submitted a Complete Response to the Not-Approvable letter on 5/27/04, to which the Division responded with a further Not-Approvable action letter on 7/27/04. A Dispute Resolution Request package was then submitted directly to Dr R. Temple. Dr Temple concluded that the key deficiency in this application, the lack of substantial evidence of efficacy, had been adequately addressed in the original NDA and subsequent amendments.

The Agency approved the submission on 10/27/04. However the application was approved without a confirmed proprietary name. The Agency has received a number of reports of prescribing and dispensing errors apparently resulting from confusion between the names "Reminyl®" and "Amaryl®;" Amaryl® is an oral anti-diabetic drug; at least 2 of these instances have led to patient deaths. In response to these errors, the DMETS staff recommended earlier that the name "Reminyl® ER" not be approved for the modified release formulation.

The sponsor requested the meeting to discuss potential proprietary names for the modified release formulation and their clinical conversion plan. In the briefing document, the sponsor submitted pharmacokinetic data and a simulation study to

support converting patients already taking Reminyl IR to the modified release formulation without a titration period.

Recommendation

After reviewing the submitted pharmacokinetic (phase 1 bioavailability and simulation data) and clinical data (GAL-INT-21), the Office of Clinical Pharmacology and Biopharmaceutics concurs with the sponsor that the patients can be converted from twice-daily Reminyl IR formulation to the once-daily modified-release formulation without additional titration.

Sponsor's Basis for Not Recommending Titration

The sponsor recommendation for not titrating patients is based on both pharmacokinetic and clinical data.

Pharmacokinetic data: The sponsor submitted both bioavailability and simulated pharmacokinetic data to support their recommendation.

Compared to the 12-mg IR tablet administered twice-daily, values for C_{max}, AUC_{24h} and C_{min} were lower for the once-daily 24-mg ER capsule. However, the 90% CI of the LS mean treatment ratio for AUC_{24h} and C_{min} met the criteria for bioequivalence. For C_{max}, bioequivalence criteria was not met; the LS mean treatment ratio and 90% CI were 0.76 (71%-80%).

Nonstochastic pharmacokinetic simulations showed that on the first day of switching from the IR formulation to the ER formulation, there was less than 5% difference in values for C_{max} and AUC. However, C_{min} value for the ER formulation was approximately 18% lower.

Clinical data: GAL-INT-10 study showed comparable effectiveness (ADAS-cog and ADCS-ADL) when comparing subjects treated with once-daily ER and twice-daily IR galantamine formulations at 26 weeks. In the open-label extension study to GAL-INT-10, subjects taking the twice-daily IR formulation were switched to the once-daily ER formulation using a titration schedule. Compared to subjects maintained on the once-daily ER formulation, similar effectiveness was observed at 6 months.

Comments

- 1) Both the bioavailability and simulated data show that subjects receiving the once-daily ER formulation have slightly lower exposure to galantamine compared to subjects receiving the twice-daily IR formulation.
- 2) The simulated pharmacokinetic data suggests that there is similar exposure to galantamine on the first day of switching from the twice-daily IR formulation to the once-daily ER formulation with respect to AUC_{24h} and C_{max}. C_{min} was approximately 19% lower for the ER formulation.
- 3) This slightly lower exposure does not appear to be clinically significant because the effectiveness trial (GAL-INT-10) showed comparable effectiveness endpoints when comparing the two formulations at 26 weeks.

- 4) Drug effectiveness appeared to be maintained in the open-label study when subjects taking the twice-daily IR formulation of galantamine were switched to the once-daily ER formulation.

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/s/

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