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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-615

Clinical Pharmacology and Biopharmaceutics Review

Addendum to Review

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION – MAJOR AMENDMENT – MULTIPLE DISCIPLINES

NDA:	21-615
Submission Type:	(AZ) Major Amendment – Multiple Disciplines (Complete Response to Non-Approval Letter)
Submission Date(s):	December 15, 2004 (e-mail) October 27, 2004
Brand Name	Reminyl Extended Release Capsules
Generic Name	Galantamine Modified Release Capsules
Reviewer	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Acting Team Leader	Sally Yasuda, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
ORM division	Division of Neuropharmacologic Drug Products (DNDP) HFD-120
Sponsor	Johnson & Johnson Pharmaceutical Research & Development / Janssen Pharmaceuticals Titusville, NJ
Formulation(s); Strength(s)	Modified Release Capsules; 8 mg, 16 mg, 24 mg
Route(s) of Administration	Oral
Indication(s)	Alzheimer's Disease

1 EXECUTIVE SUMMARY

In an e-mail dated Wednesday, December 15, 2004 the sponsor requested clarification for the interim dissolution specifications and the phase IV commitment for additional dissolution data.

The e-mail from the sponsor as well as previous e-mails are included in **Appendix 1**.

The reason for the sponsor's confusion was that the interim dissolution specifications and phase IV commitment sent in the approvable letter were inconsistent with earlier e-mail communications, (see **Appendix 2** for the dissolution specifications and phase IV commitment from this letter).

On December 16, 2004 an e-mail clarifying the information that is needed was sent to the sponsor, and a follow-up telephone conversation was held between this reviewer and Dr. James H. Medley of J&JPRD, (see **Appendix 3** for the text of this e-mail).

Final wording for the dissolution method, interim specifications, and phase IV commitments to be sent in a letter to the sponsor may be found in **section 2 Comments to Sponsor**.

Additional comments from the telephone conversation and the intent behind the final wording for the letter may be found in **section 3 Reviewer Comments**.

2 COMMENTS TO SPONSOR

2.1 Dissolution Method and Specifications

Please adopt the following **interim** dissolution method and specifications for all strengths of Galantamine HBr Modified Release Capsules.

Table 1 Interim Dissolution Method and Acceptance Criteria

Apparatus:	USP Type II Paddle apparatus
Medium:	[ ]
Volume:	[ ]
Temperature:	[ ]
Rotation Speed:	50 [ ] rpm
Sampling Times:	1, 4, and 12 hours
Specifications	1 hour: [ ]% 4 hours: [ ]% 12 hours: NLT [ ]
Acceptance Criteria:	As per USP26-NF21S2 <724> Acceptance Table 1

2.2 Phase IV Commitments

The sponsor is requested to commit to provide additional dissolution data within 6 months of approval to set final dissolution specifications. Data should include samples at the following times:

1, 4, 8, 10, 11, and 12 hours as well as content uniformity

Since the pivotal clinical batches would now have been in storage for a significant time, new batches may be used. However they must have dissolution profiles that are similar to the batches used in the pivotal clinical studies (i.e. Study GAL-INT-10, pellet batch 00I06/F54, capsule batches 00I12/F56 and 00I13/F057).

3 REVIEWER COMMENTS

It is anticipated that the 1 and 4 hour specifications will not change and only the last sampling time will change, however specifications at all sampling times are considered interim until all specifications are final.

The content uniformity from the pivotal phase III batches did not match dissolution data from any time point reported for these batches in the original NDA. Neither was the source of this information reported in the original NDA. Consequently, it's unclear whether the content uniformity was generated from a later sampling time, e.g. —hours, or from a totally different experiment. Although content uniformity is requested for the phase IV commitment, the sponsor was advised that the sampling time at which it is generated should be the same as was used to generate data for the pivotal phase III batches.

The batch(es) providing data for the 10 and 11 hour samples should also provide data at all other sampling times specified. The 10 or 11 hour data is expected to support a final sampling time and the other time points are needed to bridge this batch to the pivotal clinical efficacy batches.

Bridging to the pivotal clinical efficacy batches requires that the batches used must have dissolution profiles that are similar to the batches used in the pivotal clinical studies (i.e. Study GAL-INT-10, pellet batch 00I06/F54, capsule batches 00I12/F56 and 00I13/F057).

The sponsor requested clarification of 'similar' and was advised that this was a review issue. However, it was explained to the sponsor that mean dissolution data at each sampling time within [ ] of the mean values for the pivotal clinical batches along with similar variability is expected. In addition, the closer to the mean values from the pivotal clinical batches the better. Based upon the stability batch data and the pivotal bioequivalence batch data from the original NDA this should be achievable as it appears that the sponsor had a very reproducible manufacturing process. Examples of 'similar' batches may be found in tables 13 and 14 of the OCPB original NDA review.

Use of batches with dissolution values close to the limits of the interim acceptance criteria are not appropriate, as these batches would not be sufficiently similar to the original pivotal clinical efficacy batches.

The sponsor wanted to submit data dissolution from all commercial batches produced as part of the fulfillment of this commitment. The sponsor was told that they may provide data from all production batches, however only a single batch that is sufficiently similar to the pivotal efficacy batches is needed. A specific number of batches is not requested as this might be construed as obliging FDA to base specifications on a specific number of batches even if it is inappropriate to do so. Which batches will be used to set final specifications is a review decision. However, if the sponsor provides data from all production batches, all the data will be examined as part of the validation of the sponsor's production method, i.e. with a sufficiently sensitive method and proper specifications we expect up to — of batches may need to go to L2 testing.

A summary of all potential dissolution sampling schemes and acceptance discussed internally and with the sponsor may be found in **Appendix 4**.

4 SIGNATURES

/S/

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D. — Date

Senior Reviewer
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Sally Yasuda, Pharm.D. — Date

Acting Team Leader
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

CC List:

NDA 21-615 (orig., 1 copy)
HFD-120 (ManiR, KatzR, RzeszotarskiJ, GriffisM)
HFD-860 (KavanaghR, YasudaS, BawejaR, MehtaM, RahmanA)

Appendix 1 December 15, 2004 E-mail and Prior E-mails

-----Original Message-----

From: Medley, Jim [PRDUS] [mailto:JMedley@PRDUS.JNJ.COM]
Sent: Wednesday, December 15, 2004 3:21 PM
To: Melina Griffis (E-mail)
Cc: Foy, Suzanne [PRDGB]; Merchant, Susan [PRDUS]
Subject: FW: N21-615
Importance: High

On February 5th, 2004, J&J PRD received an e-mail from OCPB recommending the following interim specifications

1 hour	[ ] %
4 hour	[ ] %
12 hour* interim	NLT[ ]

*Data at additional time points will be needed to set a final time point. The data provided suggests that an appropriate third time point might be as low as 10 hours. Consequently, evaluation at 10, 11, and 12 hours is appropriate.

As indicated in our response, dated October 27th, 2004, we have implemented the above dissolution specifications as proposed by OCPB. Since the 12-hour time point is interim, we are also testing at 10 and 11 hours, as recommended by OCBP, on all lots that have been manufactured since that time. These limits are based on the dissolution data provided in the stability section of the NDA for 12 batches at — minutes, [ ] hours.

We have reviewed the FDA December 14th, 2004 request for a Phase IV commitment and note that dissolution data for more time points are now required, within 6 months of approval, to enable final dissolution specifications to be set. As a result of this request, we seek clarity from FDA on the following points:

1. Does the agency agree that current interim dissolution specifications are those J&J PRD agreed to in our October 27th, 2004 response?

2. To address the December 14th, 2004 Phase IV commitment request, we could collect dissolution data at [ ] hours to set the final time point if this is considered more appropriate by FDA. Does FDA agree to this proposal?

3. Based on the dissolution profiles provided in the stability section of NDA 21-615 would the agency agree that an [ ] final dissolution sampling time is too early for — , of the drug to be released from the formulation, and hence, can we exclude it from the data collection?

Please forward these questions to the Biopharm Review Team for their review and comment. Before we can provide our Phase IV commitment, we need clarification upon these points.

Please call me or email me if you have any questions. We will be available for a teleconference at your convenience.

Thanks,
Jim

Best Regards,
James H. Medley, Ph.D.
Associate Director, Global Regulatory Affairs
US Regulatory Liaison, Reminyl

Johnson & Johnson Pharmaceutical Research and Development, LLC. Ph. (609) 730-3049 Fax (609)-730-2069 Jmedley@prdus.jnj.com

-----Original Message-----
From: Griffis, Melina [mailto:GriffisM@cder.fda.gov]
Sent: Tuesday, December 14, 2004 3:32 PM
To: 'Merchant, Susan [PRDUS]'
Cc: Medley, Jim [PRDUS]
Subject: N21-615

Hi Susie,

As discussed below is the requested Phase V commitment for NDA 21-615:

To commit to provide additional dissolution data within 6 months of approval to set final dissolution specifications. Data to include multiple data points over the first — hour to define the dissolution properties of the immediate release bead component of the formulation, the 1 and 4 hour samples and samples at 8,— 10, 12, and — hours to determine a final sampling time, and data at — as well as content uniformity. New batches may be used; however, they must have dissolution profiles that are similar to the batches used in the pivotal clinical batches (i.e. Study GAL-INT-10, pellet batch 00106/F54, capsule batch 00112/F56 and 00113/F057).

****

Melina Griffis, R.Ph, LCDR-USPHS
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, FDA
(301) 594-5526
(301) 594-2858 (fax)
melina.griffis@fda.hhs.gov (email)

-----Original Message-----
From: Mille, Merril J [mailto:MILLEM@cder.fda.gov]
Sent: Thursday, February 05, 2004 2:42 PM
To: Medley, Jim [PRDUS]
Subject: RE: N21-615, Biopharm Comments

Jim,

SUBJECT: Reminyl ER Tablets/NDA 21-615

J&J REQUEST

Request for feedback on the following two points:

1. Confirm the time points for the dissolution test (i.e. 12 hours [ ]), and

2. Confirm the dissolution specification limits at each time point.

OCPB RESPONSE

OCPB's final recommendation with regard to interim specifications with regard to the above two items are as follows.

Sampling Point Sampling Time Proposed Specification

1st	1 hour	[ ]%
2nd	4 hour	[ ]%
3rd	12 hour Interim*	NLT[ ]%

* Data at additional time points will be needed to set a final time point. The data provided suggests that an appropriate third time point might be as low as 10 hours. Consequently, evaluation at 10, 11, and 12 hours is appropriate.

Respond to Ms. Melina Griffis if further info is needed.

Merril J. Mille, R.Ph.
Consumer Safety Officer
Phone: (301) 594-5528
Fax: (301) 594-2859
E-Mail: MilleM@cder.fda.gov

<<N21-615, Biopharm Comments>>

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Appendix 2 Comments to the Sponsor and Phase IV Commitments from Original NDA Review

4.1 Comments to Sponsor

1.1.1. Comments to be Conveyed

1.1.1.1. Dissolution Method and Specifications

Please adopt the following **interim** dissolution method and specifications for all strengths of Galantamine HBr Modified Release Capsules.

Table 2 Interim Dissolution Method and Acceptance Criteria

Apparatus:	USP Type II Paddle apparatus
Medium:	[ ]
Volume:	[ ]
Temperature:	[ ]
Rotation Speed:	50 [ ] rpm
Sampling Times:	1, 4, and 12 hours
Specifications	1 hour: [ ] % 4 hours: [ ] % 12 hours: NLT[ ]%
Acceptance Criteria:	As per USP26-NF21S2 <724> Acceptance Table 1

1.1.1.2. General Comments

OCPB has no general comments for the sponsor.

4.2 Phase IV Commitments

The sponsor is requested to commit to provide additional dissolution data within 6 months of approval to set final dissolution specifications. Data should include multiple data points over the [ ] hour to define the dissolution properties of the immediate release bead component of the formulation, the 1 and 4 hour samples and samples at 8, [ ] 10, 12, and [ ] hours to determine a final sampling time, and data at [ ] hours as well as content uniformity. Since, the pivotal clinical batches would now have been in storage for a significant time, new batches may be used. However they must have dissolution profiles that are similar to the batches used in the pivotal clinical studies (i.e. Study GAL-INT-10, pellet batch 00I06/F54, capsule batches 00I12/F56 and 00I13/F057).

Appendix 3 December 16, 2004 E-Mail Clarifying Phase IV Commitment

From: Kavanagh, Ronald E
Sent: Thursday, December 16, 2004 4:14 PM
To: Griffis, Melina
Cc: Yasuda, Sally; Kavanagh, Ronald E
Subject: RE: N21-615 - Response

Question 1:

We are in agreement regarding the interim specifications at 1, 4 and 12 hours.

Questions 2 and 3:

With regards to questions 2 and 3 we recommend dissolution data be generated at the following times:

1, 4, 8, 10, 11, 12, hours and content uniformity

A brief synopsis of our rationale follows:

We do not believe the 1 and 4 hour sampling times or specifications will change, however this information is needed for comparison to the pivotal phase III efficacy study batches for which 1 and 4 hour data is available.

We anticipate that the 8 hour and 12 hour sampling times will most likely not be appropriate 3rd sampling times for the final method, and we believe the appropriate time will most likely be between [redacted] hours.

In generating data to support the 3rd sampling time for a final method, 10 and 11 hour sampling times as recommended in our e-mail of February 5th, 2004 should be examined.

The 8 and 12 hour data should also both be generated to a) provide late phase dissolution data to compare to the pivotal phase III efficacy study batches for which 8 and 12 hour data is available, and b) to fulfill interim dissolution specifications.

We are unsure what time point you used to establish content uniformity for the pivotal phase III clinical batches and for the stability studies. However we anticipate that you will continue to use the same sampling time.

If any additional clarification is needed, please contact us.

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
12/17/04 10:08:53 AM
BIOPHARMACEUTICS

Sally Yasuda
12/22/04 04:00:29 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION – MAJOR AMENDMENT – MULTIPLE DISCIPLINES

NDA:	21-615
Submission Type:	(AZ) Major Amendment -- Multiple Disciplines (Complete Response to Non-Approval Letter)
Submission Date(s):	October 27, 2004
Brand Name	Reminyl Extended Release Capsules
Generic Name	Galantamine Modified Release Capsules
Reviewer	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Acting Team Leader	Sally Yasuda, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
ORM division	Division of Neuropharmacologic Drug Products (DNDP) HFD-120
Sponsor	Johnson & Johnson Pharmaceutical Research & Development / Janssen Pharmaceuticals Titusville, NJ
Formulation(s); Strength(s)	Modified Release Capsules; 8 mg, 16 mg, 24 mg
Route(s) of Administration	Oral
Indication(s)	Alzheimer's Disease

1 EXECUTIVE SUMMARY

1.1 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) immediate release oral tablets (N21-169) by JANSSEN PHARMA, for 'the treatment of mild to moderate dementia of the Alzheimer's type'.

The starting dose of REMINYL® is 4 mg twice a day (8 mg/day) with meals. The dosage may be increased by 8 mg/day in two divided doses at 4 week intervals to a maximum of 16 mg BID (32 mg/day). Doses above 16 mg /day produce a greater incidence of AEs and do not show statistically better efficacy.

On February 23, 2003 an NDA, (NDA 21-615), was submitted for a modified release capsule formulation to allow once daily dosing. Since this was a modified release product of a drug substance that had previously been shown to be efficacious only a single pivotal efficacy study was required, (GAL-INT-10).

Office of Clinical Pharmacology and Biopharmaceutics found the HPBIO section of this application acceptable. An **interim** dissolution method and specification was proposed by OCPB and a phase IV commitment for additional dissolution data to set a final specification was proposed by OCPB.

However, the Division of Neuropharmacologic Drug Products found the NDA not approvable due to **Lack of Substantial Evidence of Effectiveness**. Specifically the regulatory standard for a demonstration of effectiveness for treatment of Alzheimer's Disease is the showing of statistically significant superiority to placebo on both of two co-primary efficacy measures: a cognitive measure and a global/functional measure.

In the pivotal efficacy study, GAL-INT-10, the sponsor used the Alzheimer's Disease Assessment Scale-cognitive subscale, (ADAS-cog), for the cognitive measure and the Clinician's Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus) for the global/functional measure. Unfortunately, Reminyl ER was not superior to placebo on the CIBIC-Plus, (p=0.22).

Subsequent to the non-approval an end of review meeting was held with the sponsor and 3 approaches to respond to the non-approval were discussed, a) a PK-PD association, b) a reanalysis of the data with a compelling argument why the *a priori* specified end point should be disregarded, and c) an additional 3 month efficacy study.

In May 2004 a complete response with the second approach using data reanalysis was submitted. In response a second not approvable letter was issued at the end of July 2004.

The sponsor then requested a dispute resolution meeting in August 2004 and a meeting package was submitted in September 2004. Based upon this package it was determined that there was substantial evidence of efficacy and the sponsor was advised to submit a complete response to the 2nd not approvable letter referencing this finding and including the sponsor's proposed final labeling, (see Table 1).

Table 1 Regulatory History of Non-Approval Decision

Date	Submission or Activity Description	Comments
February 24, 2003	NDA Submission	
December 23, 2004	Not Approvable Letter	
January 06, 2004	End of Review Meeting Request by Sponsor	Proposed approaches a) PK-PD association b)reanalysis of the data with a compelling argument why the *a priori* specified end point should be disregarded c) an additional 3 month efficacy study
January 30, 2004	Meeting Package Submission	
February 05, 2004	e-mail Re: Dissolution Specification	
February 17, 2004	End of Review Meeting	
February 25, 2004	Meeting Minutes Sent to Sponsor	
May 27, 2004 June 11, 2004	Complete Response to Not Approvable Letter	Reanalysis of Data including alternative secondary global functional measurement ADCS-ADL
July 27, 2004	2nd Not Approvable Letter	
August 2, 2004	Dispute Resolution Meeting Request (with DNPDP & Dr. Temple) by Sponsor	
September 3, 2004	Dispute Resolution Meeting - Meeting Package Submission	
September 17, 2004	Internal meeting with Dr. Temple.	Dispute Resolution Meeting with Sponsor Scheduled for Sept. 22nd Canceled.
September 27, 2004	Dispute Resolution Meeting - Meeting Package Submission Forwarded to and Received by Dr. Temple's Office	Package appears to have been date stamped internally as Sept 24, 2004
October 26, 2004	Dr. Temple's Response to Dispute Resolution Request Sent to Sponsor	Dr. Temple concluded that substantial evidence of efficacy had been provided. However, a complete response to the July 27, 2004 Not Approvable letter is needed and should reference this decision to address the deficiencies cited in the Not Approvable letter and include proposed labeling for review.

Concurrent with the non-approval discussions, communications were also ongoing regarding prescription and dispensing errors due to the similarity of Reminyl (galantamine) 4 mg, 8 mg, and 12 mg to Amaryl (glimepiride) 1 mg, 2 mg, 4 mg, an oral hypoglycemic agent, and a proposed risk management program. In addition to similarity with respect to sound and the look of hand written prescriptions both Reminyl ER and Amaryl will be dosed once daily and both have 4 mg dose strengths. Finally, memory problems with Alzheimer's and the risk of hypoglycemia in potentially poorly nourished elderly make these mix-ups life threatening, with one death reported so far.

A summary of interactions between the FDA and the sponsor could not be found. However the following is a summary of internal records and information submitted by the sponsor in the current submission, (see Table 2).

Table 2 Regulatory History of Risk Management Related to Tradename

Date	Description
March 04, 2004	Consult from Division of Medication Errors and Technical Services (DMETS) and DDMAC
July 21, 2004	Notification of Prescribing and Dispensing Errors
August 2, 2004	Mtg between sponsor DNPDP & DMETS
August 13, 2004	Follow-up Telephone Conference with sponsor
August 26, 2004	Sponsor's Submission of proposed Risk Management Program (RMP)
September 28, 2004	Amendment to RMP addressing additional comments

1.1.1 SUBJECT OF THIS APPLICATION

The current application deals with the following subjects:

a) Complete Response to Lack of Substantial Evidence of Effectiveness.

b) Proposed Labeling

c) Dissolution Specifications and Phase IV Commitment with Respect to Dissolution

d) Tradename and Risk Management Program

1.2 ISSUES ADDRESSED

However, this review will only address those issues under the purview of OCPB, i.e.:

a) Dissolution Specifications and Phase IV Commitment with Respect to Dissolution

b) Labeling with Respect to Clinical Pharmacology

1.3 RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA #21-615 Amendment AZ for Galantamine HBr 8 mg, 16 mg, and 24 mg Modified Release Capsules submitted October 27, 2004, and finds this application acceptable.

Comments should be communicated to the sponsor as appropriate:
(See Section 2.1.1 on page 4).

Labeling comments should also be communicated to the sponsor as appropriate:
(See Section 2.3 Labeling Comments on page 5).

2 INFORMATION FOR COMMUNICATION TO SPONSOR

2.1 COMMENTS TO SPONSOR

2.1.1 COMMENTS TO BE CONVEYED

2.1.1.1 Dissolution Method and Specifications

Please adopt the following **interim** dissolution method and specifications for all strengths of Galantamine HBr Modified Release Capsules.

Table 3 Interim Dissolution Method and Acceptance Criteria

Apparatus:	USP Type II Paddle apparatus
Medium:	[ ]
Volume:	[ ]
Temperature:	[ ]
Rotation Speed:	50[ ] rpm
Sampling Times:	1, 4, and 12 hours
Specifications	1 hour: [ ] % 4 hours: [ ] % 12 hours: NLT[ ] %
Acceptance Criteria:	As per USP26-NF21S2 <724> Acceptance Table 1

2.1.1.2 General Comments

OCPB has no general comments for the sponsor.

2.2 PHASE IV COMMITMENTS

The sponsor is requested to commit to provide additional dissolution data within 6 months of approval to set final dissolution specifications. Data should include multiple data points over the first[ ] hour to define the dissolution properties of the immediate release bead component of the formulation, the 1 and 4 hour samples and samples at 8, [ ]10, 12, and [ ]hours to determine a final sampling time, and data at

~ hours as well as content uniformity. Since, the pivotal clinical batches would now have been in storage for a significant time, new batches may be used. However they must have dissolution profiles that are similar to the batches used in the pivotal clinical studies (i.e. Study GAL-INT-10, pellet batch 00I06/F54, capsule batches 00I12/F56 and 00I13/F057).

2.3 LABELING COMMENTS

Labeling comments in three column format follow:

The following editorial marks are used in the labeling comments to indicate various changes:

Single underline is the reviewer's proposed addition to sponsor's proposed labeling

Single ~~strikethrough~~ is the reviewer's proposed deletion to sponsor's proposed labeling

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

3 SIGNATURES

/S/

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D. — Date

Senior Reviewer
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Sally Yasuda, Pharm.D. — Date

Acting Team Leader
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

CC List:

NDA 21-615	(orig., 1 copy)
HFD-120	(ManiR, KatzR, RzeszotarskiJ, GriffisM)
HFD-860	(KavanaghR, YasudaS, BawejaR, MehtaM, RahmanA)
CDR	(Barbara Murphy)

4 REVIEW

4.1 DISSOLUTION SPECIFICATIONS AND PHASE IV COMMITMENT WITH RESPECT TO DISSOLUTION

The proposed dissolution specifications and phase IV commitment with respect to dissolution remains unchanged from the OCPB review, (October 08, 2003), for the original NDA submission, (submission date February 24, 2003).

In January 2004 the sponsor inquired regarding possible dissolution specifications for use in developing an *in vitro – in vivo* correlation. In an e-mail dated February 5th, 2004, FDA provided the proposed interim dissolution specifications and indicated that additional data would be needed if final specifications were ever set. Wording regarding a phase IV commitment was intentionally avoided as the application was non-approvable at that time. The text of the sponsor's request and FDA's February 5th reply are included in Appendix 1.

In the present submission the sponsor explicitly accepts these interim specifications stating: *"we agree to accept the proposed dissolution specifications provided by the reviewing division in the email sent on February 5, 2004."*

Furthermore, the sponsor explicitly accepts dissolutions specifications as shown in Table 4 and Table 5.

Table 4 Sponsor's Agreed to Interim Dissolution Specifications

Parameter	Technique	Sampling Time	Limits (% LC)[a,b]
Dissolution	HPLC	1 hour	[redacted]
		4 hours	[redacted]
		12 hours	nlt —%

a %LC – percent of labeled content
b nlt – not less than

Table 5 Sponsor's Stated Application of Agreed to Interim Dissolution Specifications

Specifications for:	Code	Test Method
Galantamine HBr CR Pellets eq. to — mg/g	F054	F/D/0891/02
Galantamine HBr CR Capsules eq. to 8 mg galantamine	F075	F/D/0923/01
Galantamine HBr CR Capsules eq. to 16 mg galantamine	F076	F/D/0924/01
Galantamine HBr CR Capsules eq. to 24 mg galantamine	F077	F/D/0925/01

Since the full regulatory dissolution method and the phase IV commitment have not yet been forwarded to the sponsor these should now be forwarded as stated in Section 2.1 Comments to Sponsor Subsection 2.1.1.1 Dissolution Method and Specifications, and Section 2.2 Phase IV Commitments.

4.2 LABELING

The sponsor's proposed labeling of interest to OCPB remains unchanged from the original NDA submission, and OCPB has no new major comments.

There are some minor points of clarification that OCPB has made. Consequently there are minor differences between OCPB's original labeling comments in the original OCPB NDA review and the present review. A list of these minor differences follow:

- Clarification of a paragraph division in the Dosage and Administration Section based on the sponsor's inclusion of a draft of their proposed final printed labeling.
- Clarification of unchanged text by addition of ellipses in the OCPB proposed labeling.
- Clarification of OCPB's comments.

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On Original

Appendix 1 E-mail Communications Regarding Dissolution Specifications

From: Mille, Merril J [mailto:MILLEM@cder.fda.gov]
Sent: Thursday, February 05, 2004 2:42 PM
To: Medley, Jim [PRDUS]
Subject: RE: N21-615, Biopharm Comments

Jim,

SUBJECT: Reminyl ER Tablets/NDA 21-615

J&J REQUEST

Request for feedback on the following two points:

1. Confirm the time points for the dissolution test (i.e. 12 hours or — hours), and

2. Confirm the dissolution specification limits at each time point.

OCPB RESPONSE

OCPB's final recommendation with regard to interim specifications with regard to the above two items are as follows.

Sampling Point	Sampling Time	Proposed Specification
1st	1 hour	[redacted]
2n	4 hour	[redacted]
3rd	12 hour Interim*	NLT —%

* Data at additional time points will be needed to set a final time point. The data provided suggests that an appropriate third time point might be as low as 10 hours. Consequently, evaluation at 10, 11, and 12 hours is appropriate.

Respond to Ms. Melina Griffis if further info is needed.

Merril J. Mille, R.Ph.
Consumer Safety Officer
Phone: (301) 594-5528
Fax: (301) 594-2859
E-Mail: MilleM@cder.fda.gov

-----Original Message-----
From: Medley, Jim [PRDUS] [mailto:JMedley@PRDUS.JNJ.COM]
Sent: Tuesday, January 13, 2004 2:50 PM
To: Mille, Merril J
Cc: Griffis, Melina; Yao, Caiping [PRDUS]
Subject: N21-615, Biopharm Comments

Merril,

Please ask the Dr. Bauweja to confirm for us the time points for the dissolution test (i.e. 12 hours or — hours) and please confirm the dissolution specification limits at each time point. We are finalizing our study report for the IVIVC study and we need the time points and limits to complete that report.

Thank you,
Jim Medley

Best Regards,
James H. Medley, Ph.D.
Associate Director, Global Regulatory Affairs
US Regulatory Liaison, Reminyl
Johnson & Johnson Pharmaceutical Research and Development, LLC.
Ph. (609) 730-3049
Fax (609)-730-2069
Jmedley@prdus.jnj.com

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Sally Yasuda
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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
NEW DRUG APPLICATION – END OF REVIEW MEETING - NOTES

NDA:	21-615	**Sponsor:**	Johnson & Johnson Pharmaceutical Research & Development / Janssen Titusville, NJ
Drug: **[Tradename]**	Reminyl Extended Release Capsules	**Drug:** **[Generic]**	Galantamine Modified Release Capsules
Strength(s) Formulation(s):	8 mg, 16 mg, 24 mg Modified Release Capsules	**Indication(s)**	Alzheimer's Disease
Correspondence Date / **Date Received:**	January 30, 2004 February 2, 2004	**Type of Submission:**	End of Review Meeting -Meeting Package
Date of Internal Pre-Meeting:	February 12, 2004	**Date of Meeting with Sponsor:**	February 17, 2004

1 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 starting dose of REMINYL® IR tablets and solution is 4 mg twice a day (8 mg/day) with meals. The dosage may be increased by 8 mg/day in two divided doses at 4 week intervals to a maximum of 16 mg BID (32 mg/day). Doses above 16 mg /day produce a greater incidence of AEs and do not show statistically better efficacy.

In NDA 21-615 submitted February 24, 2003, the sponsor applied for approval of an extended release capsule formulation for once daily administration. As part of this application the sponsor submitted the results of a 3-way study comparing Placebo, Reminyl IR Tablets, and Reminyl ER Capsules. In this study both Reminyl IR Tablets and Reminyl ER Capsules failed to beat placebo on one of the pre-specified co-primaries.

2 QUESTION OF INTEREST TO OCPB

Given the similarity with respect to the two formulations in affecting clinical outcomes and in consideration of the biopharmaceutical similarities, we would like to discuss an alternative approach to approval based upon an appropriate demonstration of the link between the pharmacokinetic profile and the pharmacological response. The rationale for such an approach is based on the following:

(i) the PK profiles of Reminyl IR and ER formulations differ in plasma Cmax but do not differ in AUC 24h or Cmin,.

(ii) the similarity in efficacy in the cognitive and functional domains between the IR and ER formulations suggests that efficacy is not driven by Cmax although this hypothesis has not been tested.

Is the Division amenable to this?

3 COMMENTS

In order to use this approach there would need to be a well defined PK-PD relationship, which there is not. In addition, the hypothesis that pharmacodynamic effect is related to Cmin has not been proven. (See **Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, USDHHS/FDA/CDER, April 2003.**)

4 SIGNATURES

/S/

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D. **Date**

Reviewer
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Raman Baweja, Ph.D. **Date**

Team Leader
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

CC List:

NDA 21-615	(orig., 1 copy)
HFD-120	(ManiR, OlivaA, KatzR, ReszotarskiJ, MilleM)
HFD-860	(KavanaghR, BawejaR, MehtaM, SahajwallaC)
CDR	(Barbara Murphy)

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Ron Kavanagh
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Raman Baweja
4/2/04 03:02:23 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
NEW DRUG APPLICATION - REVIEW

NDA:	21-615
Submission Date(s):	February 24, 2003
Brand Name	Reminyl Extended Release Capsules
Generic Name	Galantamine Modified Release Capsules
Reviewer	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Team Leader	Raman Baweja, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
ORM division	Division of Neuropharmacologic Drug Products (DNDP) HFD-120
Sponsor	Johnson & Johnson Pharmaceutical Research & Development / Janssen Titusville, NJ
Formulation(s); Strength(s)	8 mg, 16 mg, 24 mg Modified Release Capsules
Route(s) of Administration	Oral
Indication(s)	Alzheimer's Disease

1 EXECUTIVE SUMMARY

1.1 BACKGROUND

1.1.1 MECHANISM OF ACTION, AVAILABILITY, AND APPROVED INDICATION

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'.

1.1.2 DOSAGE AND ADMINISTRATION

The starting dose of REMINYL® is 4 mg twice a day (8 mg/day) with meals. The dosage may be increased by 8 mg/day in two divided doses at 4 week intervals to a maximum of 16 mg BID (32 mg/day). Doses above 16 mg /day produce a greater incidence of AEs and do not show statistically better efficacy.

1.1.3 ADME

Both the solution and immediate release (IR) tablets are well absorbed with an absolute bioavailability of approximately 90% - 100% and a Tmax of approximately 1 hour. Galantamine has low protein binding and a volume of distribution of approximately 2.5 L/kg. Other approximate values for pharmacokinetic metrics include 6 hours for half-life and 300 ml/min clearance with ¾ of the dose eliminated by hepatic metabolism and 1/4 eliminated by renal clearance. Virtually all absorbed parent drug and metabolites are

recovered in the urine. Metabolism is primarily by CYP2D6, CYP3A4 and glucuronidation. Metabolism is summarized in Table 1.

Table 1 Summary of Galantamine Metabolism

Species	Activity / Relative Potency	Relative Circulating Concentrations	Urinary Recovery
Galantamine	1	39% - 77%	32%
galantamine glucuronide	—	14% - 24%	12%
Norgalantamine	Active	≤ 10%	—
Epigalanthamine	<1%	—	—
Galanthaminone	<1%	—	—
O-desmethyl-galantamine	—	—	—
O-desmethyl-norgalantamine	—	—	—

Mean differences in exposures of approximately 30% higher have been reported in women, the elderly and in poor metabolizers, with no reported difference by race or ethnicity. However, the number of subjects were either inadequate or CYP2D6 status was unknown. In general we can say that for these groups, intergroup differences are not large (~30%) and don't require dosage adjustments.

1.1.4 SUBJECT OF THIS APPLICATION

The present application is for a modified release capsule formulation to allow once daily dosing.

1.2 ISSUES ADDRESSED

What is the Proposed New Formulation?

The proposed modified release capsule formulation consists of an encapsulated tri-layer pellet with the following layers progressing from the outer to inner layers:

a) Immediate Release (IR) Drug Layer [ ] of dose)
b) Rate controlling membrane layer
c) Controlled Release Drug Layer coated sugar spheres [ ] of dose)

The 3 proposed strengths of 8 mg, 16 mg, and 24 mg differ only in the amount of encapsulated pellets.

What is the Relative Bioavailability Compared to the Immediate Release Tablets?

Extent of absorption is similar between the MR and IR formulations upon both single dosing and steady-state dosing with the highest proposed strength capsule. In contrast the peak concentrations are intentionally lower for the MR capsules ([ ] lower) and Tmax is longer (study medians 3.5 – 5 hours) as compared to the IR tablets (median 1 hour).

There are no consistent differences in half-life across studies between the MR and IR formulations that could be attributable to flip-flop kinetics.

Figure 1 Comparative Mean Steady-State Concentration vs. Time Profiles for Galantamine IR Tablets 12 mg BID and Galantamine MR Capsules 24 mg QD.

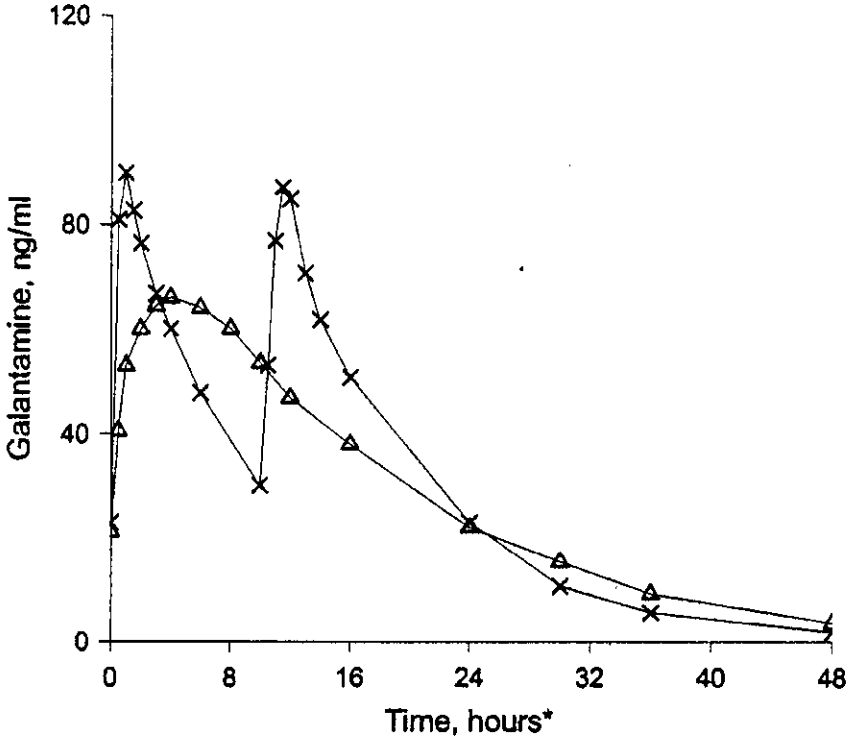


Figure 2 Individual and Mean Steady-State Concentration vs. Time Profiles for Galantamine IR Tablets 12 mg BID.

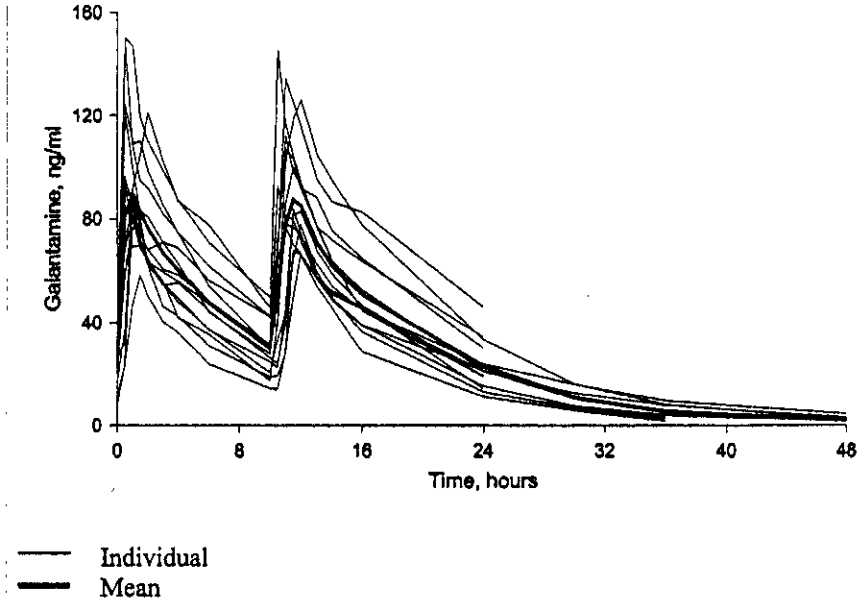
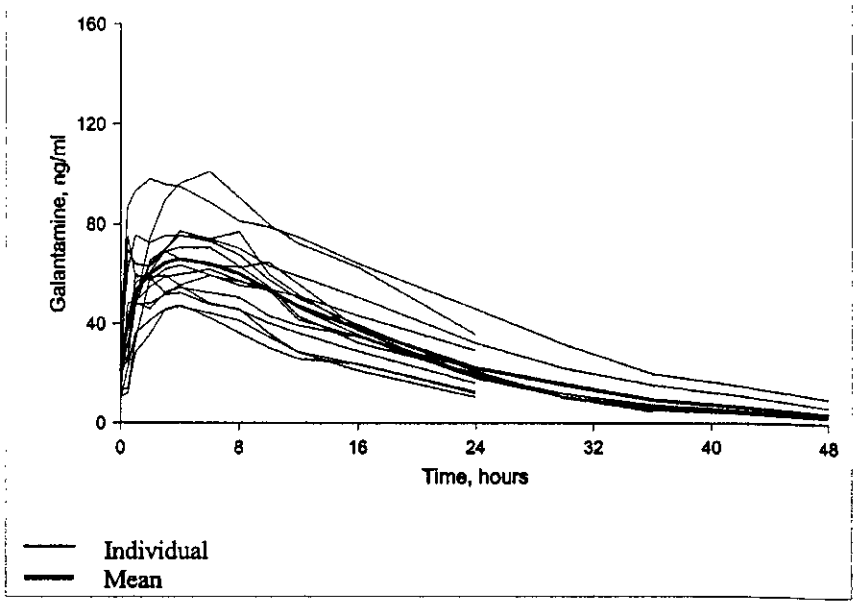


Figure 3 Individual and Mean Steady-State Concentration vs. Time Profiles for Galantamine MR Capsules 24 mg QD.



Is it Dose Proportional and Time Invariant?

Upon multiple dosing of the modified release capsule dose proportionality is observed from 8 to 24 mg per day and there is no evidence of time invariance.

Is there a Food Effect?

No food effect was observed on the extent of absorption when the highest strength to be marketed 24 mg MR capsule was examined. However, there are changes in the rate of absorption consistent with a slight increase in initial lag time possibly due to delayed gastric emptying followed by a slightly more rapid absorption rate. These changes in absorption metrics include a delay in Tmax, (median delay 1 hour from 4.0 to 5.0 hours) and a 12% higher Cmax for the MR capsule in the presence of food.

The Cmax of the MR capsule is approximately 70 -75% of the IR tablet when both are administered under fasting conditions, and 85% of the IR tablet when the MR capsule is administered under fed conditions as compared to the IR tablet taken when fasted. However, comparison of the IR tablet under fed and fasted conditions show no difference in the extent of absorption, with a delay in median Tmax from 1.0 to 2.5 hours and a 25% decrease in Cmax.

The sponsor is proposing that the MR capsule be taken under fed conditions, similar to the current labeling for the IR tablet. Thus a patient switching from the IR tablet to the MR capsule while taking each as directed with food will have Cmaxs with the MR capsule that are approximately 13% higher than the morning Cmax with the IR tablet, and Tmaxs that occur at approximately 5 hours as compared to 2.5 hours.

Is there an Age Effect?

Pharmacokinetics of the MR formulation was compared in healthy elderly and young adults.

Table 2 Age Statistics of Elderly and Young Adults in Study GAL-NED-9[a]

Elderly	Young Adults
68.8 ± 3.8 (5.6) 65 - 80 [67]	38.0 ± 11.4 (30.0) 22 - 55 [35]

a Values are Mean ± SD, (%CV), range, [median] years.

When controlled for CYP2D6 genotype there is no effect of age on galantamine pharmacokinetics.

Is there a Gender Effect?

Gender effect was not examined with the MR capsule; although a gender effect explainable by weight differences have been reported for the IR tablet.

Most studies included approximately equal numbers of male and female subjects and reported pharmacokinetics metrics unstratified for gender. As the intent of this submission was to establish bioequivalence, even if there is a gender effect the use of crossover study designs should keep the gender effect consistent between study arms provided that there is not a large interaction between the rate of absorption and gender on bioavailability. The results of studies with the two formulations showed they were equivalent with respect to mean extent of absorption and that variability was not excessive.

Is there an effect of Race or Ethnicity?

There were too few subjects in studies to examine the effect of race or ethnicity. Differences due to differences in CYP2D6 phenotype frequency with race and ethnicity is expected, however, the magnitude is not expected to be of major clinical significance.

Are the Commercial Scale Batches Bioequivalent to the Pivotal Clinical Trial Batches?

Yes.

Is the Proposed Dissolution Method Acceptable?

The sponsor has proposed [ ] buffer [ ] as the dissolution media. Proposed specifications are [ ] at 4 hours and not less than [ ] at [ ] hours.

Hydrochloric Acid [ ] was the dissolution media used for all batches used in the clinical studies and for stability studies up through — months. [ ] buffer was used from 12 months onward. As a modified controlled release formulation [ ] buffer is more appropriate than an acidic dissolution medium. In addition the sponsor has provided some data that does suggest that dissolution is nearly identical in the two media.

Are the Proposed Dissolution Specifications Acceptable?

First it should be noted that the sponsor has included a small — overage in the final manufacturing process that does not appear to be necessary.

Dissolution specifications were set based upon a commercial scale batch used in the bioequivalence study and not on the pivotal clinical trial capsules. However, mean dissolution profiles of these batches are only slightly lower.

Most problematic are the sampling times and the proposed acceptable dissolution ranges.

Dissolution profiles indicate that dissolution of the immediate release layer, which comprises — of the drug dose, is complete by — minutes with another [ ] of the dose dissolving by 1 hour. Since the most likely problem with the immediate release layer is inadequate content an earlier initial time point would likely not be any more informative and at 1 hour we do have some control over the initial dissolution of the controlled release layer. Therefore the 1 hour dissolution time point is acceptable. Since the IR component is completely dissolved by — minutes. there is no need to for the lower end of the dissolution range to be so low. So a lower limit of [ ] rounded upwards, (i.e. —), with **a range of [ ] at 1 hour** is proposed.

Mean dissolution at four hours is approximately 60% for the commercial scale batches and — for the pivotal clinical batch, although an earlier mid-point dissolution would be preferable, as there is no data between 1 and 4 hours and since 60% dissolution is acceptable as a mid-point 4 hours is an acceptable sampling time. The sponsor has proposed that the lower limit at the 4 hour sampling time be set to — as the sponsor claims this is needed to account for degradation upon storage. First, lowering the limit to account for degradation is inappropriate. Second, the lowest extent of dissolution observed for any individual capsule over all dissolution experiments at 4 hours even upon storage was [ ] and even this individual value was unusually low. Therefore **a 4 hour range of [ ] (i.e. [ ])** is adequate.

At — hours the sponsor proposes a specification of not less than (NLT) — %. For the pivotal clinical batch mean dissolution was approximately — at 8 hours, — at 12 hours, and — at — hours. This suggests that a sampling time of 10 hours is probably appropriate. However, there is no data for 10 hours. Individual data for stability experiments was not provided, however, examination of summary data

indicates that at 8 hours almost no batches would pass at the L1 level, nearly half would pass at the L2 level, and many of the remainder would likely fail. In contrast, at 12 hours all batches would pass at the L1 level. This also suggests that a sampling time of 10 hours is probably appropriate. However, as there is no data at 10 hours, a specification of **NLT — % at 12 hours** is appropriate for an **initial interim specification**.

These limits have been discussed with the sponsor.With regards to acceptance criteria this should be as per 'Acceptance Table 1' from USP section <724> for extended release formulations.

1.3 RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) have reviewed NDA #21-615 for Galantamine HBr 8 mg, 16 mg, and 24 mg Modified Release Capsules submitted February 24, 2003, and finds this application acceptable.

Comments should be communicated to the sponsor as appropriate:
(See Section 2.1.1 on page 6).

Labeling comments should also be communicated to the sponsor as appropriate:
(See Section 2.3 Labeling Comments on page 7).

2 INFORMATION FOR COMMUNICATION TO SPONSOR

2.1 COMMENTS TO SPONSOR

2.1.1 COMMENTS TO BE CONVEYED

2.1.1.1 Dissolution Method and Specifications

(Please adopt the following **interim** dissolution method and specifications for all strengths of Galantamine HBr Modified Release Capsules.

Table 3 Interim Dissolution Method and Acceptance Criteria

Apparatus:	USP Type II Paddle apparatus
Medium:	[ ]
Volume:	[ ]
Temperature:	[ ]
Rotation Speed:	50 — rpm
Sampling Times:	1, 4, and 12 hours
Specifications	1 hour: [ ]% 4 hours: [ ]% 12 hours: NLT [ ]
Acceptance Criteria:	As per USP26-NF21S2 <724> Acceptance Table 1

2.1.1.2 General Comments

OCPB has no general comments for the sponsor.

2.2 PHASE IV COMMITMENTS

The sponsor is requested to commit to provide additional dissolution data within 6 months of approval to set final dissolution specifications. Data should include multiple data points over the first —hour to define the dissolution properties of the immediate release bead component of the formulation, the 1 and 4 hour samples and samples at 8, —10, 12, and — hours to determine a final sampling time, and data at — hours as well as content uniformity. Since, the pivotal clinical batches would now have been in storage for a significant time, new batches may be used. However they must have dissolution profiles that are similar to the batches used in the pivotal clinical studies (i.e. Study GAL-INT-10, pellet batch 00I06/F54, capsule batches 00I12/F56 and 00I13/F057).

2.3 LABELING COMMENTS

Labeling comments in three column format follow:

The following editorial marks are used in the labeling comments to indicate various changes:

Single underline is the reviewer's proposed addition to sponsor's proposed labeling

Single ~~strikethrough~~ is the reviewer's proposed deletion to sponsor's proposed labeling

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

3 SIGNATURES

/S/

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D. — Date

Reviewer
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Raman Baweja, Ph.D. — Date

Team Leader
Division of Pharmaceutical Evaluation 1 (DPE1)
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Meeting:

Date:	Thursday, September 24, 2003
Time:	2:00 PM – 3:00 PM
Location:	WOC2 4th Floor Conference Room E
Level:	Required Interdivision
Attendees:	Ron Kavanagh OCPB Sr. Reviewer, Ray Baweja OCPB Team Leader, Mehul Mehta OCPB Division Director DPE-1, Chandra Sahajwalla OCPB Associate Division Director DPE-1, Arzu Selen OCPB Associate Division. Director DPE-3

CC List:

NDA 21-615	(orig., 1 copy)
HFD-120	(ManiR, OlivaA, KatzR, ReszotarskiJ, MilleM)
HFD-860	(KavanaghR, BawejaR, MehtaM, SahajwallaC)
CDR	(Barbara Murphy)

Table of Contents

4 REVIEW

4.1 CHEMISTRY

4.1.1 FORMULATION DESCRIPTION

Galantamine HBr modified release capsules are an encapsulated sustained release beaded formulation intended for once daily administration. Three strengths are submitted for review, (see Table 4).

Table 4 Proposed Strengths of Galantamine HBr Modified Release Capsules

Strength (mg base equivalents)	Formulation Code
8 mg	F075
16 mg	F076
24 mg	F077

All three capsule strengths are manufactured using a layered controlled release pellet formulation, (formulation number F054), consisting of the following layers progressing from the outer to inner layers:

a) Immediate Release (IR) Drug Layer
b) Rate controlling membrane layer
c) Controlled Release Drug Layer
d) [ ] sugar spheres coated with a Controlled Release Drug Layer

See Figure 4.

Figure 4 Schematic of Galantamine HBr Modified Release Pellet

[

]

The Immediate Release Drug Layer provides an immediate release of [ ] of the drug content. [

]

Each modified release pellet contains a drug concentration of [ ]; mg of galantamine hydrobromide per gram of pellets, which is equivalent to [ ] mg of galantamine free-base.

4.1.2 CHEMISTRY CODES

4.1.2.1 F-numbers

An F number (F for Formula) are assigned to each pharmaceutical formulation, (see Table 4).

4.1.2.2 R-number

An R-number (R for Research) refers to the number assigned to a molecule. The R-number of Galantamine HBr is R113675.

4.1.3 QUALITATIVE QUANTITATIVE COMPOSITION

The qualitative-quantitative composition of the 3 proposed strengths of galantamine modified release capsules and of the encapsulated pellet is shown in Table 5.

Table 5 Qualitative Quantitative Composition of Galantamine HBr Modified Release Capsules

Galantamine free-base Eq		8 mg	16 mg	24 mg	% (w/w) of Layer	% (w/w) of Pellet
Code		F075	F076	F077		
Ingredient	Specification	Weight (mg)				
Core						
Sugar Spheres	NF	C				
Controlled Release Drug Layer						
Galantamine HBr	In-house					
Coating	In-house					
	USP					
Rate Controlling Membrane						
Ethylcellulose,	NF					
Hypromellose	USP					
Diethyl Phthalate	NF					
Immediate Release Drug Layer						
Galantamine HBr	In-house					
Coating	In-house					
	USP					J
Fill Weight Controlled Release Pellets (F054)	—	C				J,
Hard Gelatin Capsule						
Size	—	4	2	1	—	—
Cap and Body Color	—	Pink opaque	Caramel opaque	White opaque	—	—
Imprinting:	—	GAL 8	GAL 16	GAL 24	—	—

a Current Pharmacopoeial reference or in-house method

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Although the sponsor claims that the pellet batch sizes that were used in human studies were [redacted] or nominally [redacted] kg, the information provided on the number of capsules produced does not tend support these claims, (see Table 11). However, batch records for pellet batch 01H27/001, which is claimed to be commercial scale and was used in the bioequivalence study with the pivotal clinical batches were provided and are [redacted] kg and match the batch formula in Table 6.

Table 11 Comparison of Sponsor's Claimed Pellet Batch Sizes as Compared with Reported Batch Sizes[a]

Study	Strength	Code	Lot #	# Caps	Manufacturing Site	Pellet Batch #	Pellets Batch Size
[redacted] kg Pellet Batch as Claimed by Sponsor							
GAL-BEL-19 GAL-BEL-20	8 mg	F055	99I28/F55				kg
GAL-BEL-20	16 mg	F056	99I30/F56				kg
	24 mg	F057	99J02				kg
GAL-NED-8 GAL-NED-9 GAL-INT-10[b]	8 mg	F055	00I11/F55				kg
	16 mg	F056	00I12/F56				kg
GAL-NED-8 GAL-NED-9 GAL-NED-12 GAL-INT-10[b]	24 mg	F057	00I13/F057				kg
GAL-INT-21[c]	8 mg	F055	01E03/F055				kg
	16 mg	F056	01E07/F056				kg
	24 mg	F057	01E21/F057				kg
	24 mg	F057	01E22/F057				kg
[redacted] kg Pellet Batches as Claimed by Sponsor							
GAL-NED-12	8 mg	F075	01H27/745			01H27/001	kg
	16 mg	F076	01H27/744			01H27/001	kg
	24 mg	F077	01H27/739			01H27/001	kg

a Note codes F075, F076, F077 denote 8 mg, 16 mg, and 24 mg capsules made from [redacted] kg commercial scale pellet batches and codes F055, F056, and F057 denote capsules made from [redacted] kg biobatch scale pellet batches
b Phase III Efficacy Study
c Phase III Safety Study

4.1.7 DISSOLUTION

The sponsor has proposed a dissolution method and specifications. There are several issues with the sponsor's methods for selecting the proposed dissolution method and specifications.

a) The batches that were used to set the proposed specifications are not clearly identified. It appears that batches of 8 mg, 16 mg, and 24 mg capsules, (batches 01H27/745, 01H27/744, 01H27/739), from a [ ] kg' commercial scale pellet batch (01H27/001) were used to set the proposed specifications, (see Table 11).

b) These batches were not the appropriate batches to use to set specifications as they were not used in the pivotal clinical efficacy study. Instead capsule batches 00I11/F55, 00I12/F56, and 00I13/F057 that were used in the pivotal clinical efficacy batches should have been used to set dissolution specifications (see Table 11).

c) The data provided for these capsule batches only included mean data and only for the proposed time points. However, complete dissolution profile data was available from a capsule batch used in stability experiments that were made from the same pellet batch. In addition, mean dissolution data from a pellet batch used to make capsules used in the pivotal clinical efficacy study is available. Comparison of the above data reveals minimal differences in mean dissolution between these batches. Therefore in spite of inappropriate batches being used to set specifications the results are sufficiently similar to the appropriate batches so that the data from the batches used may be relied on (see Table 14).

d) The proposed method uses [ ] buffer, whereas the data used for setting the dissolution specifications used [ ] hydrochloric acid. In addition, the use of hydrochloric acid medium was switched to [ ] buffer in the middle of the stability experiments. However, the sponsor does provide a comparison of the methods that indicate that the results in either medium should be interchangeable.

e) The lower end of the proposed specification for the early time point, (i.e. — at 1 hour), is [ ] of the content of the IR component (— of LC) that should have completely dissolved by that time.

f) The sponsor inappropriately widened the lower end of the proposed specification for the midpoint sample by —) adjust for dissolution changes observed on storage.

g) Based upon complete dissolution profiles from the stability study it appears that sampling times are selected in such a manner as to limit their utility as a quality control measure. In addition, to this the dissolution profile data suggests that additional sampling times such as —and 10 hours should have been investigated.

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4.1.7.1 Sponsor's Proposed Dissolution Method & Specifications

The sponsor's proposed dissolution methods, specifications and acceptance criteria are shown in Table 12.

Table 12 Sponsor's Proposed Dissolution Methods and Specifications for Galantamine HBr MR Pellets (F054) and 8 mg (F075), 16 mg (F076) and 24 mg (F077) Capsules

Apparatus	USP Type II Paddle apparatus
Medium:	[ ]
Volume:	[ ]
Temperature:	[ ]
Rotation speed:	50 – rpm
Detection:	[ ]
Sampling Times:	1, 4, and ● hours
Proposed Specifications	1 hour: [ ], 4 hours: [ ] % – hours: NLT –%
Acceptance Criteria	Not mentioned

4.1.7.2 Change in Dissolution Method

According to the sponsor the dissolution medium was changed from [ ] hydrochloric acid to [ ] buffer because of oxidative degradation of galantamine [ ] to [ ] which is formed in an acidic environment. Galantamine and [ ] are shown in side by side for comparison in Figure 5 and Figure 6.

Figure 5 Galantamine

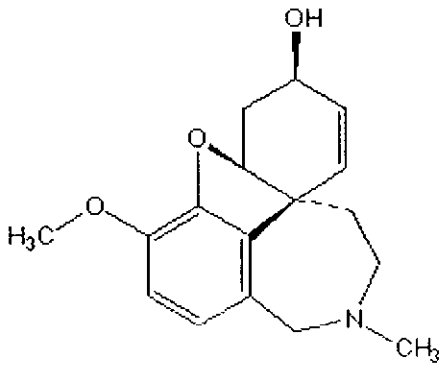

Figure 6 Degradation Product [ ]

[ ]

This change in procedure methods were instituted after [ ] of stability data had been generated. Thus dissolution data from [ ] of storage onward are generated in [ ] buffer and prior to this in hydrochloric acid. As a modified release dosage formulation [ ] buffer is more appropriate to use as a dissolution medium than hydrochloric acid.

4.1.7.2.1 Comparison of Dissolution Methods [ ] · Buffer vs. HCl)

As shown by the comparative dissolution data in [ ] HCl and [ ] Buffer shown in Table 13, dissolution appears similar in both media. In addition, — minute dissolution data from the stability studies conducted prior to and after — months of storage, (see APPENDIX 3), indicate that dissolution of the immediate release layer is essentially complete by — minutes regardless of the dissolution media. Consequently, the information provided tends to indicate that the proposed media is acceptable.

Table 13 Comparative Dissolution Data in [ ] and [ ]

Description	Batch No.[a]	Storage Conditions	Sampling Time	Results (%) 1 hour	4 hours	— hours	1 hour	4 hours	—nours
MR Pellets Used in Pivotal Phase III Clinical Study (GAL-NED-10)	00I06/F054	?	Assay Method	F/D/0891/01/00 [ ] HCl			F/D/0891/02/00 [ ] Buffer —		
			N	6	6		6	6	
			Mean ± SD (%CV) Range [Median]	29.9 ± 0.5 (1.5) [29.8]	61.6 ± 0.9 (1.5) [61.6]		30.6 ± 0.4 (1.3) [30.4]	63.7 ± 0.7 (1.2) [63.9]	
8 mg Capsules (From — kg Commercial Size Batches Used in Stability Experiments)	00J10/F075	?	Assay Method	F/D/0923/01/00 [ ] HCl			F/D/0923/01/01 [ ] Buf		
			N	6	6		6	6	
			Mean ± SD (%CV) Range [Median]	28.8 ± 1.4 (4.8) [28.8]	59.4 ± 1.8 (3.0) [59.8]		27.7 ± 1.4 (5.1) [27.7]	58.1 ± 1.8 (3.2) [57.7]	
	00J11/F075		Assay Method	F/D/0923/01/00 [ ] HCl			F/D/0923/01/01 [ ] Buf		
			N	6	6		6	6	
			Mean ± SD (%CV) Range [Median]	28.2 ± 0.9 (3.2) [27.9]	59.9 ± 1.3 (2.2) [60.1]		28.2 ± 1.1 (4.1) [27.7]	62.0 ± 2.4 (3.8) [61.5]	

a Note codes F075, F076, F077 denote 8 mg, 16 mg, and 24 mg capsules made from — kg commercial scale pellet batches and codes F055, F056, and F057 denote capsules made from — kg biobatch scale pellet batches.

4.1.7.3 Supporting Data for Sponsor's Dissolution Method and Specifications

According to the sponsor the proposed dissolution specifications are based on the mean dissolution data from full scale batches — kg) used in the bioequivalence study between the — kg and — kg scale batches, (study GAL-NED-12), rather than the pivotal clinical trial capsules.

The sponsor's supporting data for the dissolution specifications is shown in Table 14. In addition, mean dissolution data from the — kg biobatch scale pellets, (batch # 00I06/F54 used to manufacture the 8 mg, 16 mg, and 24 mg capsules used in the pivotal phase III clinical study, (GAL-INT-10), are also shown in Table 14 and in Figure 7 for comparison.

The sponsor states that the 'specified ranges were set based on the recommendations in the available Guidance documents, ICH Q6A and FDA Guidance for Industry Extended Release Oral Dosage Forms.

At the 1 hour time point the sponsor proposes an acceptance range of [ ].

At the 4 hour time point the sponsor's proposal begins with a baseline acceptance range of [ ] The sponsor then lowers the lower limit of the acceptance criteria by [ ]. 'based on the observed stability trend'. More specifically the sponsor states: "A slight retardation in dissolution is observed in the dissolution profile during storage in the different packaging materials. The decrease is mostly pronounced in [ ] blister at [ ] Packaging materials used in stability experiments include HDPE bottles and the aforementioned blisters.

The sponsor then proposes an \ hour acceptance criteria of not less than —

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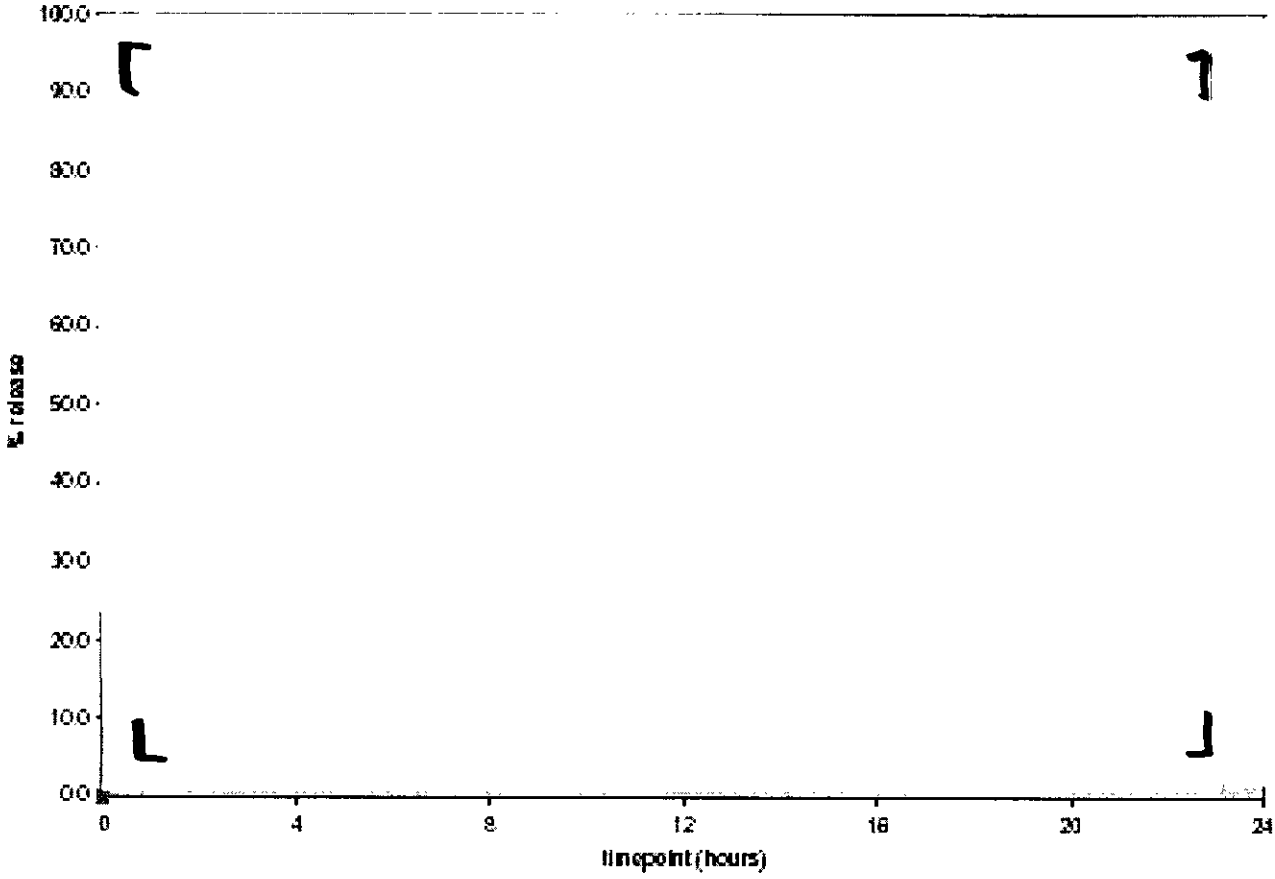
Figure 7 Dissolution Profile for Galantamine HBr MR Pellet Batch (00I06/F54) — 'g biobatch) used in Pivotal Phase III Clinical Study (GAL-INT-10)



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4.1.7.4 OCPB's Initial Counter Proposal

Additional data for these pivotal clinical batches at these 3 sampling times are shown in Table 15. This more complete data for the pivotal clinical batches indicates that at each time point the % dissolved is slightly higher than the batch used by the sponsor. Based upon this data the specification should be [ ] at 1 hour, [ ] at 4 hours and NLT [ ] at some later time point. However, the initial OCPB counterproposal was further refined as follows:

These data, (see Table 15), indicate that dissolution of the immediate release layer, which comprises [ ] of the drug dose, is complete by — minutes with another [ ] of the dose dissolving by 1 hour. Since the most likely problem with the immediate release layer is inadequate content an earlier initial time point would likely not be any more informative and at 1 hour we do have some control over the initial dissolution of the controlled release layer. Therefore the 1 hour dissolution time point is acceptable. Since the IR component is completely dissolved by — minutes, there is no need to for the lower end of the dissolution range to be so low. Thus a range of [ ] at 1 hour was initially proposed.

Mean dissolution at four hours is approximately 62% for the pivotal clinical batches and — for the commercial scale batches used in the bioequivalence study. Although an earlier mid-point dissolution would be preferable, as there is no data between 1 and 4 hours and since 62% dissolution is acceptable as a mid-point 4 hours is an acceptable sampling time. The sponsor has proposed that the lower limit at the 4 hour sampling time be set to — as the sponsor claims this is needed to account for degradation upon storage. However, lowering the limit to account for degradation on storage is inappropriate. Second, the lowest extent of dissolution observed for any individual capsule over all dissolution experiments at 4 hours even upon storage was — and even this individual value was unusually low. Therefore a 4 hour range of [ ] is adequate and could even be higher.

At [ ] hours the sponsor proposes a specification of not less than (NLT) [ ] For the pivotal clinical batch mean dissolution was approximately — at 8 hours, — at 12 hours, and — at — hours (see Table 14). This suggests that a sampling time of 10 hours is probably appropriate; however, there is no data for 10 hours. Individual data for stability experiments was not provided, however, examination of summary data indicates that at 8 hours almost no batches would pass at the L1 level, nearly half would pass at the L2 level, and many of the remainder would likely fail. In contrast, at 12 hours all batches would pass at the L1 level. This also suggests that a sampling time of 10 hours is probably appropriate. However, as there is no data at 10 hours, a specification of NLT [ ]% at 12 hours is appropriate for an initial specification.

With regards to acceptance criteria this should be as per 'Acceptance Table 1' from USP section <724> for extended release formulations.

N.B. Information on the stability batches and the stability dissolution data can be found in APPENDIX 3. Although different method numbers are used their differences are limited to the capsule strength, with the exception that the dissolution media was changed at [ ] and thereafter.

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4.1.7.4.1 Discussion of Dissolution Specifications with Sponsor

The sponsor was informed of the initial regulatory dissolution specifications in a teleconference with OCPB on September 16, 2003. A summary of the sponsor's initial proposal, OCPB's counter-proposal and the data it was based on, and the sponsor's response is shown in Table 16.

Table 16 Summary of Dissolution Proposals Discussed with the Sponsor in Teleconference held September 16, 2003.

	Sample Time			Comments
	1 hr	4 hr	hr	
Sponsor's Initial Proposal			NLT	—
Pivotal Clinical Batch Data	IR by hr MR by 1 hr)			Data suggests that a specification of NLT could be achieved in the 12 hr range
Initial OCPB Proposal to Sponsor			12 hr	Acceptance Criteria as per As per USP26-NF21S2 <724> Acceptance Table 1
Sponsor's Counter Proposal			hr interim	Sponsor claimed that they would be unable to achieve the OCPB proposal based on extrapolated stability data that has not been submitted.

The sponsor was informed that their counterproposal would be discussed, however dissolution specifications are set based upon the dissolution characteristics of pivotal clinical efficacy study of pivotal bioequivalence study batches, and that expiry dating is then determined from these specifications.

4.1.7.4.2 Review of Sponsor's Counterproposal for Dissolution

In consideration of the sponsor's concerns, the pivotal clinical batch data and the stability data that had been submitted was reexamined.

Figure 8 shows the global mean and range of dissolution values observed for all individual capsules in stability studies under ambient conditions for up to — months with the —kg batches using the clinical trial formulation. (The — months of data from the — kg commercial formulation batch are not shown). This graph indicates that after an initial decrease in dissolution in the — months, that dissolution then stabilizes and that there are further no changes in dissolution with time. Secondly, this graph shows that for each of OCPB's 3 initial proposed sampling specifications/times that even at — months that the lowest dissolution value observed is several percent greater than the lower limit of the proposed acceptance range.

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4.1.8 BIOANALYSIS

Bioanalysis was performed by either LC/MS/MS or HPLC with Fluorescence Detection. Each study reported a different analytic method, however upon inspection the 'validation reports' were actually in-process quality control reports for the clinical samples. As shown in Table 19 the analytical methods were the same or very similar across studies. In process variability and bias appeared to be acceptable, although as no validation reports were provided, there is a lack of stability or selectivity/specificity data. Presumably this was provided with the original NDA for galantamine and was found to be acceptable.

Table 19 Bioanalytical Methods by Study

Study	Analytical Method	Validation Report	Analytical Method
GAL-NED-8	LC/MS/MS	R113675/53	(Date: May 03, 2001): Standard Analytical Method for human plasma
GAL-NED-9	LC/MS/MS	R113675/54	(Date: May 03, 2001): Standard Analytical Method for human plasma
GAL-NED-12[a]	LC/MS/MS	R113675/055	(Date: 5 October 2001)
GAL-BEL-17	HPLC Fluorescence	R113675/040	Janssen Accession No. N122079/2 (Revised Version of N122079) (Date: Feb 11, 1998)
GAL-BEL-18	HPLC Fluorescence	R113675/044	
GAL-BEL-19	HPLC Fluorescence	R113675/JPL002101	(Date: June 5, 1998)
GAL-BEL-20	HPLC Fluorescence	R113675/JPL001005	(Date: January 24, 2000)

a Pivotal bioequivalence study

4.2 PHARMACOKINETICS

4.2.1 SUMMARY OF HUMAN STUDIES

Human studies submitted in support of N21-615 for galantamine HBr MR capsules are shown in Table 20.

Table 20 Human Studies Submitted in Support of N21-615 for Galantamine HBr MR Capsules

Protocol No.	Study Title
Formulation Development Studies	
GAL-BEL-17	Oral bioavailability of galantamine after single 8-mg doses as two sustained-release tablet formulations and as a mini-osmotic pump capsule with galantamine in solution in comparison with a 4-mg immediate-release tablet administered b.i.d. in healthy subjects.
GAL-BEL-18	Oral bioavailability of galantamine after single 8-mg doses as a sustained-release formulation taken with and without food in comparison with a 4-mg immediate-release tablet administered b.i.d. under fasting conditions in healthy subjects.
GAL-BEL-19	Oral bioavailability of galantamine after single 8-mg doses as two sustained-release formulations in comparison with a 4-mg immediate-release tablet administered b.i.d. in healthy subjects.
Clinical Pharmacology & Pharmacokinetic Studies	
GAL-BEL-19	*See above*
GAL-BEL-20	A repeated-dose galantamine trial in healthy subjects to compare the steady-state bioavailability between a once-daily 24 mg slow-release (SR) formulation and a 12 mg immediate-release (IR) tablet administered twice daily, and to explore the dose-proportionality of the 8, 16 and 24 mg o.d. SR formulation.
GAL-NED-8	Food effect on steady-state galantamine pharmacokinetics of the 24-mg q.d. controlled-release capsule and comparison of steady-state galantamine bioavailability between the controlled-release capsule and the immediate-release tablet.
GAL-NED-9	Pharmacokinetics and dose proportionality of galantamine controlled-release capsules after repeated oral dosing in healthy elderly and young subjects
GAL-NED-12	Steady-State Bioequivalence of the 24-mg Controlled-Release Galantamine Clinical Research Capsule and the To-Be-Marketed Capsule
Phase III Efficacy and Safety Studies	
GAL-INT-10	Placebo-Controlled Evaluation of Galantamine in the Treatment of Alzheimer's Disease: Safety and Efficacy of a Controlled-Release Formulation
GAL-INT-21	An Open-Label Extension Study to Assess the Long-Term Safety of a Controlled-Release Formulation of Galantamine HBr in the Treatment of Alzheimer's Dementia

A summary of all pharmacokinetic and clinical pharmacology studies performed, along with formulation descriptions and a brief description of the sponsor's study objectives and conclusions are shown in Table 21.

Table 21 Summary of Biopharmaceutic / Clinical Pharmacology Development Program

Study	Goal	Formulation					Study Objective(s)	Study Conclusions
		Code[a]	Description	Ethylcellulose : Hydroxy-propyl-methylcellulose Ratio (EC : HPMC)	Coating Thickness	Strength		
GAL-BEL-17	Evaluation of 2 different initial pilot MR formulations	F021	Encapsulated MR Coated Pellets			8 mg	Comparative bioavailability of 1 x 8 mg MR capsule relative to 2 x 4 mg IR tablets given 8 hours apart	Bioequivalent with respect to extent of absorption
		F023	Encapsulated MR Coated Pellets			8 mg		Low bioavailability relative to IR tablets
GAL-BEL-18	Evaluation of a new pilot formulation with faster release characteristics	F044	Encapsulated Combination of MR Pellets and IR tablet [redacted]			8 mg	Comparative bioavailability of 1 x 8 mg MR capsule relative to 2 x 4 mg IR tablets given 8 hours apart. Evaluation of food effects	Frel = 92% (90% CI: 89 - 96%) No effects of food on Frel.
GAL-BEL-19	Evaluation of a pilot formulation with pellets that contain both an IR and a MR component.	F055	SR and IR components combined in the same pellet as two layers separated by a rate controlling membrane in [redacted]			8 mg	Comparative bioavailability of 1 x 8 mg MR capsule relative to 2 x 4 mg IR tablets given 8 hours apart.	Comparable bioavailability relative to IR tablets with respect to AUC, but with a lower Cmax.
	Same as above but faster release	F063				8 mg		Bioequivalent to IR tablets with respect to both AUC and Cmax
GAL-BEL-20	Clinical Trial Formulations	F055				8 mg	Comparative steady-state bioavailability of 24 mg MR capsule qd relative to 12 mg IR tablets BID administered 10 hours apart. Dose proportionality at steady-state of 8 mg, 16 mg, and 24 mg MR capsules	Frel = 92% (90% CI: 88 - 95%) Cmax GMR = 0.7 with delayed Tmax. Dose proportional.
		F056				16 mg		
		F057				24 mg		
GAL-NED-8	"	F057	"	"	"	24 mg	Food effect at steady-state on highest to-be-marketed MR capsule and bioavailability relative the IR tablet.	Lack of significant food effect with approximately 11% increase in both AUC and Cmax. Still bioequivalent with respect to AUC, and still bioinequivalent with respect to Cmax.
GAL-NED-9	Clinical Trial Batch	F055				8 mg	Age effect and dose proportionality	Dose proportional in both age groups. CYP2D6 poor metabolizers had elevated exposures No age effect when groups are controlled for CYP2D6 metabolizer status.
		F056				16 mg		
		F057				24 mg		
GAL-NED-12	Clinical Trial Batch	F057	"	"	"	24 mg	Steady-State bridging study of clinical trial and commercial batch sizes.	Bioequivalent
	Commercial Batch	F077						

a Note codes F075, F076, F077 denote 8 mg, 16 mg, and 24 mg capsules made from [redacted] kg commercial scale pellet batches and codes F055, F056, and F057 denote capsules made from [redacted] kg biobatch scale pellet batches.

4.2.2 SINGLE DOSE PHARMACOKINETICS

4.2.2.1 Comparative Pharmacokinetics to IR Tablet Formulation

With single 8 mg doses, the selected modified release capsule formulation is bioequivalent to the IR tablet formulation with respect to extent of absorption, although the peak concentrations and Tmax are intentionally lower and more prolonged, (see Table 22) compared to the IR tablets.

4.2.3 MULTIPLE DOSING

4.2.3.1 Comparative Pharmacokinetics to IR Tablet Formulation and Dose Proportionality

Upon multiple dosing of the modified release capsule dose proportionality is observed from 8 to 24 mg per day. In addition, the bioequivalence profile of the highest strength capsule with respect to the IR tablet observed at steady-state is similar to the profiles observed with single doses (see Table 23, Table 24, Figure 1, Figure 2, and Figure 3).

Table 22 Comparative Pharmacokinetic Metrics of Two Pilot Galantamine Modified Release Capsule Formulations and the Approved Immediate Release Tablets (Study GAL-BEL-19)

Metrics	Descriptive Statistics[a]			Geometric Mean Ratios (90% CI)	
	Treatment A	Treatment B	Treatment C		
	Test Formulation 1 (F55) (CTF/TBM Formulation)[b]	Test Formulation 2 (F63)	Reference Formulation (F13)		
	8 mg MR cap SD	8 mg MR cap SD	Two 4 mg IR Tabs 8 hours apart	A:C	B:C
Tmax (hours)	4.8 ± 0.5 (10.4) [5.0]	4.6 ± 0.5 (10.9) [5.0]	1.1 ± 0.4 (36.4) [1.0]	—	—
Cmax (ng/ml)	20.6 ± 5.0 (24.3) [21.6]	25.5 ± 5.8 (22.7) [24.1]	23.7 ± 5.4 (22.8) [22.2]	—	—
	20.0	24.9	23.2	86 78 - 96	107 98 - 119
Cmin (ng/ml)	—	—	8.15 ± 2.22 (27.2) [7.76]	—	—
Tmax2 (hours)	—	—	9.2 ± 0.7 (7.6) [9.0]	—	—
Cmax2 (ng/ml)	—	—	33.6 ± 8.9 (26.5) [29.6]	—	—
AUC_∞ (ng/ml x hr^{-1})	378 ± 152 (40.2) [352]	395 ± 137 (34.7) [348]	370 ± 102 (27.6) [353]	—	—
	352[c]	375[c]	357[c]	99 93 - 104	105 99 - 111
Frel	99.6 ± 16.0 (16.1) [98.3]	106 ± 10 (16.1) [104]	—	—	—
kel (hr^{-1})	0.0923 ± 0.0230 (24.9) [0.0989]	0.104 ± 0.018 (17.3) [0.111]	0.113 ± 0.025 (22.1) [0.112]	—	—
$t_{1/2}$ (hours)	8.1 ± 2.5 (30.9) [7.0]	6.9 ± 1.4 (20.3) [6.3]	6.4 ± 1.5 (23.4) [6.2]	—	—

a Mean ± SD (CV%) Min – Max (Median)
b CTF/TBM – Clinical Trial / To-Be-Marketed Formulation
c Geometric Mean

Table 23 Steady-State Dose Proportionality and Comparative Pharmacokinetic Metrics of The To-Be-Marketed Galantamine Modified Release Capsule Formulations and the Approved Immediate Release Tablets (Study GAL-BEL-20)

Parameter	A	B	C	D	Treatment A	Treatment B	Treatment C	Treatment D
	n	n	n	n	galantamine 8 mg MR caps po qd x 7 days	galantamine 16 mg MR caps po qd x 7 days	galantamine 24 mg MR cap po qd x 7 days	galantamine 12 mg IR tab po bid x 7 days
$C_{predose}$ Day 6 (ng/ml)	16	16	15	15	8.08 ± 3.76 (46.5) [7.08]	15.9 ± 7.9 (49.7) [15.6]	24.9 ± 15.6 (2.7) [18.5]	25.7 ± 14.2 (55.3) [22.8]
Day 7								
$C_{predose}$ (ng/m)l*	16	16	15	14	7.22 ± 3.75 (51.9) [6.03]	15.3 ± 7.4 (48.4) [12.8]	21.1 ± 8.8 (41.7) [20.0]	22.9 ± 10.8 (47.2) [21.5]
Tmax (Hr)*	16	16	15	14	4.0 ± 1.8 (45.0) [4.0]	3.5 ± 2.2 (62.9) [3.5]	3.5 ± 1.9 (54.3) [4.0]	0.9 ± 0.4 (44.4) [1.0]
Cmax (ng/ml)*	16	16	15	14	24.7 ± 6.3 (25.5) [23.3]	48.6 ± 12.2 (25.1) [44.7]	68.6 ± 16.3 (23.8) [69.7]	101 ± 27 (26.7) [92.6]
Cpredose (ng/ml)**	NA	NA	NA	14	—	—	—	30.1 ± 11.0 (36.5) [28.6]
Tmax (Hr)**	NA	NA	NA	14	—	—	—	11.3 ± 0.5 (4.4) [11.3]
Cmax (ng/ml**	NA	NA	NA	14	—	—	—	96.7 ± 24.9 (25.7) [88.3]
C_{24} (ng/ml)	16	16	15	14	7.33 ± 3.76 (51.3) [6.80]	16.2 ± 7.1 (43.8) [15.5]	22.1 ± 9.7 (43.9) [19.9]	23.1 ± 9.7 (42.0) [21.1]
AUC_{24h} (ng/ml x hr^{-1})	16	16	15	14	393 ± 123 (31.3) [364]	782 ± 243 (31.1) [724]	1102 ± 315 (28.6) [1076]	1240 ± 354 (28.5) [1151]
Css_{av} (ng/ml)	16	16	15	14	16.4 ± 5.1 (31.1) [15.2]	32.6 ± 10.1 (31.0) [30.2]	45.9 ± 13.1 (28.5) [44.8]	51.7 ± 14.7 (28.4) [48.0]
Frel(C/ D)	NA	NA	14	NA	—	—	92.0 ± 8.0 (8.7) [92.3]	—
Fl (%)	16	16	15	14	112 ± 22 (19.6) [109]	108 ± 21 (19.4) [106]	107 ± 17 (15.9) [103]	163 ± 30 (18.4) [170]
t½ (hrs)	NA	NA	7	7	--	--	8.3 ± 1.8 (21.7) [7.9]	6.9 ± 1.9 (13.0) [6.4]

Table 24 Comparative Steady-State Bioavailability of the Highest Strength of the To-Be-Marketed Galantamine Modified Release Capsule Formulation and the Approved Immediate Release Tablets (Study GAL-BEL-20)

Metrics	Geometric Means		Geometric Mean Ratios C:D (90% CI)
	Treatment C	Treatment D	
	Galantamine 24 mg MR Capsule po QD x 7 days*	Galantamine 12 mg IR Tablet po BID x 7 days	
AUCτ (ng/ml x h^{r-1})	1062	1159	0.92 (0.88 - 0.95)
Cmax (ng/ml)	67.0	95.7	0.70 (0.64 - 0.76)
Cmin (ng/ml)	19.3	19.5	0.99 (0.90 - 1.08)

4.2.3.1.1 Food Effect

The slight increase in Cmax in conjunction with a slightly longer Tmax observed in the presence of food suggests that food may cause a slight increase in initial lag time possibly due to delayed gastric emptying followed by a slightly more rapid absorption rate. However, any food effect present is not expected to be clinically significant as it would increase Cmax in the direction of the higher levels seen with the IR tablet. (see Table 25).

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Table 25 Food Effect at Steady-State on Highest Strength To-Be-Marketed Galantamine HBR MR Capsule and Bioavailability Relative the IR tablet (Study GAL-NED-8)

Metrics	Descriptive Statistics			Geometric Means			Geometric Mean Ratios (90% Confidence Intervals)		
Treatments	A	B	C	A	B	C	A:C	B:C	B:A
	24 mg MR Cap QD Fasted	24 mg MR Cap QD Fed	12 mg IR Tabs BID Fasted						
n	22 / 7	22 / 8	22 / 7	22	22	22	—	—	—
AUC_{24} (ng/ml x h^{-1})	967.8 ± 193.3 (20.0) [974.6]	1015.2 ± 214.3 (21.1) [1014.7]	1050.3 ± 239.4 (22.8) [994.9]	946	989	1022	92.6 (89.7; 95.5)	96.8 (93.8; 99.8)	104.6 (101.4; 107.9)
Tmax (hr)	4.4 ± 1.7 (38.1) [4.0]	4.9 ± 1.7 (34.0) [5.0]	1.2 ± 0.6 (52.1) [1.0]	—	—	—	—	—	—
Cmax (ng/ml)	63.0 ± 12.0 (19.1) [63.6]	70.6 ± 15.0 (21.3) [67.7]	84.3 ± 21.4 (25.4) [82.1]	61.5	68.8	81.2	75.7 (71.2; 80.4)	84.6 (79.7; 89.9)	111.9 (105.3; 118.9)
Cmin (ng/ml)	18.8 ± 4.6 (24.3) [19.4]	19.9 ± 7.2 (36.0) [18.2]	21.7 ± 7.9 (36.6) [19.2]	18.1	18.6	20.3	89.3 (82.9; 96.1)	91.8 (85.2; 98.8)	102.8 (95.5; 110.7)
Cssav (ng/ml)	40.3 ± 8.1 (20.0) [40.6]	42.3 ± 8.9 (21.1) [42.3]	43.8 ± 10.0 (22.8) [41.5]	39.4	41.2	42.6	92.6 (89.7; 95.5)	96.8 (93.8; 99.8)	104.6 (101.4; 107.9)
FI (100%)	110.1 ± 11.7 (10.6) [113.2]	121.4 ± 16.6 (13.7) [120.8]	144.8 ± 35.3 (24.4) [144.4]	—	—	—	—	—	—
$t_{½}$ (hr)	8.3 ± 1.2 (14.9) [8.1]	8.0 ± 2.0 (24.7) [7.8]	8.5 ± 1.2 (14.1) [8.9]	—	—	—	—	—	—

4.2.3.1.2 Age Effect

Upon initial inspection it appears that the elderly have lower exposures to galantamine from the MR capsules. However, further analysis reveals that when subjects are stratified for CYP2D6 metabolizer genotype there is no clear effect of age, (see Table 26 and Figure 9 through Figure 11).

Table 26 Effect of Age on Galantamine HBr MR Capsule Pharmacokinetics (Study GAL-NED-9)

Metric[a]	Summary Statistics				Geometric Means				Geometric Mean Ratio (90% CI)	
	Young PM	Young EM	Young All	Elderly	Young PM	Young EM	Young All	Elderly		
Treatment	A	B	C	D	A	B	C	D	D:C	D:B
N	3	10	16	16	—	10	16	16	—	—
Cmax (ng/ml)	103.4 ± 11.0 (10.6) [97.5]	75.9 ± 10.7 (14.1) [76.8]	79.7 ± 16.7 (21.0) [77.9]	74.6 ± 14.1 (18.9) [75.6]	—	75.2	78.1	73.2	93.8 (83.0;106.0)	97.4 (86.1;110.1)
Tmax(h)	3.67 ± 0.58 (15.75) [4.00]	4.25 ± 1.82 (42.7) [4.00]	4.10 ± 1.62 (39.48) [4.00]	4.44 ± 1.46 (32.89) [4.00]	—	4.0	4.0	4.0	0.0	0.0
Cmin (ng/ml)	54.2 ± 16.3 (30.1) [60.4]	24.8 ± 8.4 (34.0) [27.0]	29.3 ± 16.4 (55.9) [30.6]	24.1 ± 7.5 (31.2) [23.6]	—	23.3	25.0	23.0	91.8 (68.6;122.9)	98.7 (77.8;125.2)
AUC24 (ng*h/ml)	1916 ± 301 (16) [1743]	1253 ± 221 (18) [1314]	1355 ± 370 (27) [1363]	1172 ± 255 (22) [1196]	—	1235	1311	1145	87.3 (75.3;101.3)	92.7 (80.1;107.2)
Css,avg (ng/ml)	79.8 ± 12.6 (15.7) [72.6]	52.2 ± 9.2 (17.7) [54.7]	48.8 ± 10.6 (21.8) [49.8]	56.4 ± 15.4 (27.3) [56.8]	—	51.5	54.6	47.7	87.3 (75.3;101.3)	92.7 (80.1;107.2)
Fluctuation Index (%)	62 ± 19 (30) [52]	100 ± 18 (18) [100]	106 ± 16 (15) [108]	95 ± 25 (26) [90]	—	—	—	—	—	—
DN AUC (ng/m/ x hr^{-1} per mg)	80 ± 13 (16) [73]	52 ± 9 (18) [55]	49 ± 11 (22) [50]	56 ± 15 (27) [57]	—	—	—	—	—	—
DN Cmax (ng/ml/mg)	4.3 ± 0.5 (10.6) [4.1]	3.2 ± 0.4 (14.1) [3.2]	3.1 ± 0.6 (18.9) [3.2]	3.3 ± 0.7 (21.0) [3.2]	—	—	—	—	—	—
DN Cmin ng/ml/mg)	2.3 ± 0.7 (30.1) [2.5]	1.0 ± 0.4 (34.0) [1.1]	1.0 ± 0.3 (31.2) [1.0]	1.2 ± 0.7 (55.9) [1.3]	—	—	—	—	—	—
DN Css,avg (ng/ml/mg	3.3 ± 0.5 (15.7) [3.0]	2.2 ± 0.4 (17.7) [2.3]	2.0 ± 0.4 (21.8) [2.1]	2.4 ± 0.6 (27.3) [2.4]	—	—	—	—	—	—
Half-life (h)	13.1 ± 2.0 (15.2) [12.7]	9.4 ± 2.2 (23.7) [8.9]	10.0 ± 1.2 (12.6) [10.2]	10.1 ± 2.5 (24.8) [9.8]	—	—	—	—	—	—

a DN – Dose normalized

Figure 9 Comparative Linear and Semi-log Plots of Mean Steady-State Galantamine Plasma Concentrations in the Young and Elderly

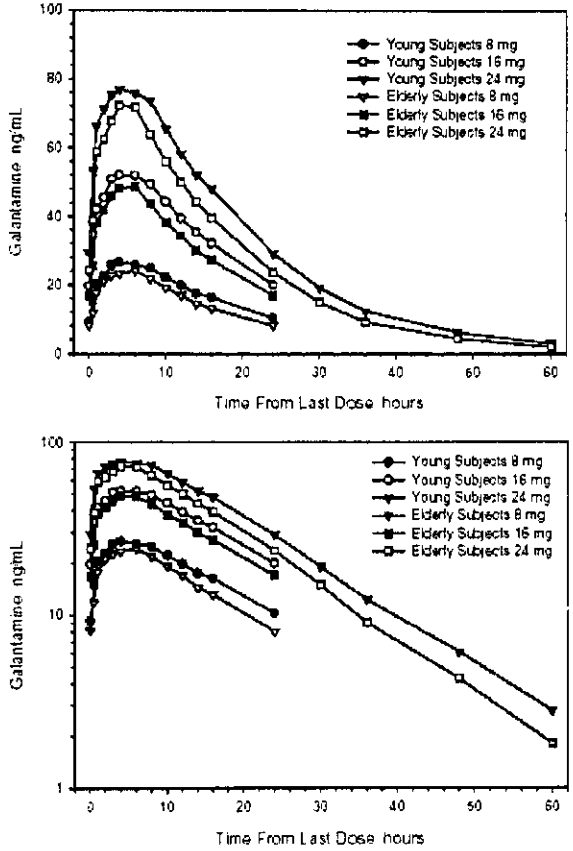


Figure 10 Comparative Linear and Semi-log Plots of Mean Steady-State Galantamine Plasma Concentrations in the Young and Elderly CYP2D6 Extensive Metabolizers

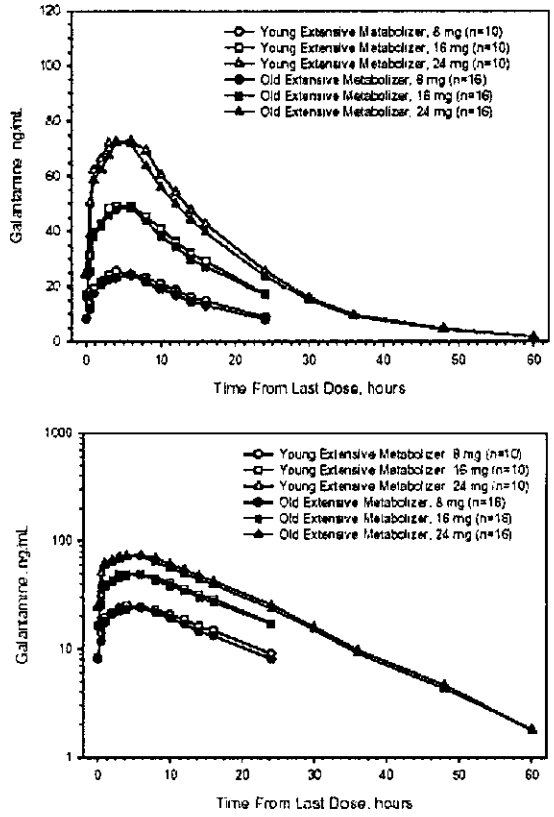
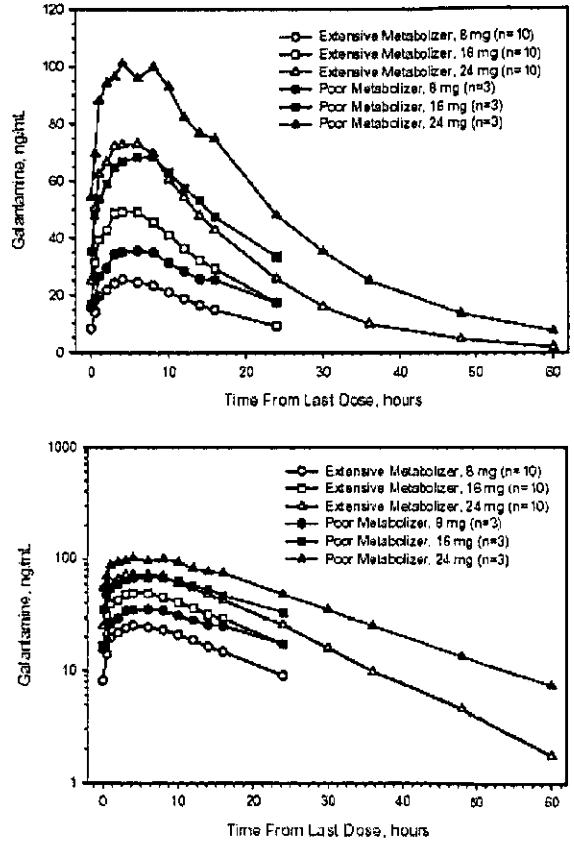


Figure 11 Comparative Linear and Semi-log Plots of Mean Steady-State Galantamine Plasma Concentrations in Young CYP2D6 Extensive and Poor Metabolizers



4.2.4 BIOEQUIVALENCE

4.2.4.1 Clinical Trial Batch and Biobatch

Since, the sponsor modified the manufacturing process upon scale up to the — kg commercial batch size, a steady-state bioequivalence study of the highest strength capsule formulation was conducted of a pivotal clinical trial batch (24 mg capsule batch 00I13/F057; — kg) and a commercial scale batch (pellet batch 01H27/001 — kg), (see Table 10 and Table 11).

The results of this study indicate that the — kg commercial scale pellet batches are bioequivalent to a pivotal — kg pellet batch, (see Table 27).

Table 27 Steady-State Bioequivalence of Pivotal Clinical Trial and Commercial Batch Sizes (Study GAL-NED-12)

Metric	Descriptive Statistics		Geometric Means		Difference	Geometric Mean Ratio (90% CI)
	Test	Ref	Test	Ref		
	Commercial Scale Batch	Pivotal Clinical Trial Batch	Commercial Scale Batch	Pivotal Clinical Trial Batch		
	[			], kg		
Cmax (ng/ml)	75.2 ± 15.8 (21.0) [76.0]	77.0 ± 16.1 (20.9) [74.1]	73.2	74.9	—	97.7 (94.1;101.5)
Tmax (h)	5.3 ± 1.4 (26.4) [6.0]	4.9 ± 1.3 (26.5) [6.0]	6.0	6.0	0.0	100.4 (83.3;108.3)
Cmin (ng/ml)	27.0 ± 10.1 (37.4) [27.1]	26.1 ± 11.2 (42.9) [23.9]	24.9	23.6	—	105.6 (98.0;113.8)
AUCτ (ng/ml x hr^{-1})	1216 ± 292 (24.0) [1231]	1245 ± 316 (25.4) [1216]	1174	1197	—	98.1 (94.5;101.7)
Css,av (ng/ml)	50.7 ± 12.2 (24.1) [51.3]	51.9 ± 13.2 (25.4) [50.7]	—	—	—	—
FI (%)	97.8 ± 18.1 (18.5) [98.0]	102 ± 17 (16.7) [101]	—	—	—	—
Swing (%)	201 ± 72 (35.8) [192]	227 ± 93 (41.0) [198]	—	—	—	—

5 APPENDICES

5.1 APPENDIX 1 SUBJECT DEMOGRAPHICS

Table 28 Summary Statistics of Subject Demographics by Study[a]

Study	Sex (M/F)	Race C/B/O[b] C/B/A/H	Smoker[c] NS/Lt SMKER/SMKER	Age (years)	Weight (kg)	Height (cm)	CYP2D6 genotype EM/PM	OC use
GAL-BEL-19	6/6	10/1/1	11/1/0	25 ± 8 (32) 19 - 43 [22]	68 ± 13 (19.1) 46 - 86 [69]	175 ± 14 (8) 155 - 195 177]	12/0	5
GAL-BEL-20	8/8	16/0/0	14/2/0	24 ± 6 (25) 20 – 44 [23]	68 ± 11 (16.2) 48 - 84 [71]	174 ± 11 (6.3) 155 - 188 [178]	15/na[d]	
GAL-NED-8	12/12	24/0/0	16/8/0	30.7 ± 7.5 (24.4) 20 - 44 [28.5]	72.9 ± 13.7 (18.8) 54 - 103 [74]	177.3 ± 11.9 (6.7) 155 - 202 [178]	20 / 2 (83.3%) / (8.3%)	
GAL-NED-12	13/11	21/1/1/1	20/5/0	36.5 ± 13.0 (35.7) 19 - 55 [36.5]	70.4 ± 11.9 (16.8) 50 - 90.5 [69.4]	173.6 ± 9.1 (5.2) 158 - 192 [172]		
	11	9/1/1/0	9/2/0	36.5 ± 14.1 (38.6) 19 - 54 [37]	77.3 ± 9.9 (12.8) 58.5 - 90.5 [78.9]	181.1 ± 6.9 (3.8) 167 - 192 [181]		
	13	12/0/0/1	10/3/0	36.5 ± 12.7 (34.6) 19 - 55 [36]	64.6 ± 10.4 (16.0) 50 - 86.9 [65.6]	167.3 ± 4.9 (2.9) 158 - 173 [170]		
GAL-NED-9	8/8	14/0/2/0	10/6/0	38.0 ± 11.4 (30.0) 22 - 55 [35]	68.8 ± 11.3 (16.5) 48 - 86 [68.5]	171.6 ± 9.9 (5.8) 157 - 192 [172]		
	9/7	15/0/0	15/1/0	68.8 ± 3.8 (5.6) 65 - 80 [67]	75.0 ± 11.2 (15.0) 49 - 91 [74]	172.4 ± 8.2 (4.7) 159 - 185 [172]		

a MEAN (SE) 95% CI) MEDIAN (MIN; MAX) (95% CI)
b Caucasian, black, other or Caucasian, black, Asian, Hispanic, other
c light smoker defined as not more than 10 cigarettes, or 2 cigars, or 2 pipes per day
d EM/PM status not available

5.2 APPENDIX 2 BATCHES USED IN PHARMACOKINETIC AND CLINICAL STUDIES

Table 29 Description of Galantamine HBr MR Capsule Batches Used in Biopharmaceutic Formulation Development Studies

Study	Manufacturing			Batch Size		Formulation Number	Strength	Drug Substance Lot	Container Closure System
	Batch Number	Site	Date	# Caps	Weight of Pellets				
GAL-BEL-17	97J17/F21	[redacted]	20-Nov-97	[redacted]	[redacted] kg	F021	8 mg	PUA051	[redacted] aluminum blister
	97J17/F23		24-Nov-97	[redacted]	[redacted] kg	F023	8 mg	PUA051	[redacted] aluminum blister
	H 954		22-May-97	[redacted] tablets	—	F013	4 mg	PUA011	[redacted] aluminum blister
GAL-BEL-18	99C11/F44	[redacted]	16-Mar-99	[redacted]	[redacted] kg	F044	8 mg	PUA121	[redacted] aluminum blister
	H 954		22-May-97	[redacted] tablets	—	F013	4 mg	PUA011	[redacted] aluminum blister

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Table 30 Description of Galantamine HBr MR Capsule Batches Used in Pharmacokinetic, Bioequivalence, and Clinical Pharmacology Studies

Study	Manufacturing			Batch Size		Formulation Number	Strength	Drug Substance Lot	Container Closure System
	Batch Number	Site	Date	# Caps	Weight of Pellets				
GAL-BEL-19	99I28/F55		28-Sep-99		kg	F055	8 mg	PUA161	aluminum blister
	99I29/F63		29-Sep-99		kg	F063	8 mg	PUA132	aluminum blister
	99GL576		2-Jul-99	tablets	-	F013	4 mg	PUA081	aluminum blister
GAL-BEL-20	99I28/F55		28-Sep-99		kg	F055	8 mg	PUA161	aluminum blister
	99I30/F56		29-Sep-99		kg	F056	16 mg	PUA161	aluminum blister
	99J02/F57		2-Oct-99		kg	F063	24 mg	PUA161	aluminum blister
	99GL578		2-Jul-99	tablets	-	F027	12 mg	PUA 131	aluminum blister
GAL-NED-8	00I11/F055		11 Sep 00		kg	F055	8 mg	PUA241	aluminum blister
	00I12/F056		10 Sep-00		kg	F056	16 mg	PUA241	aluminum blister
	00I13/F057		13 Sep-00		kg	F057	24 mg	PUA241	aluminum blister
	99GL577		2 Jul-99	tablets		F026	12 mg	PUA131	aluminum blister
GAL-NED-9	00I11/F055		11 Sep-00		kg	F055	8 mg	PUA241	aluminum blister
	00I12/F056		10 Sep-00		kg	F056	16 mg	PUA241	aluminum blister
	00I13/F057		13 Sep-00		kg	F057	24 mg	PUA241	aluminum blister
GAL-NED-12	00I13/F057		13-Sep-00		kg	F057	24 mg	PUA241	aluminum blister
	01H27/745		4-Oct-01		kg	F075	8 mg	PUA401	aluminum blister
	01H27/744		5-Oct-01		kg	F076	16 mg	PUA401	aluminum blister
	01H27/739		8-Oct-01		kg	F077	24 mg	PUA401	aluminum blister

Table 31 Description of Galantamine HBr MR Capsule Batches Used in Pivotal Clinical Efficacy and Safety Studies

Study	Manufacturing			Batch Size		Formulation Number	Strength	Drug Substance Lot	Container Closure System
	Batch Number	Site	Date	# Caps	Weight of Pellets				
GAL-INT-10 (Pivotal Clinical Efficacy Study)	00I11/F055		12-Sep-00		kg	F055	8 mg	PUA241	aluminum blister
	00I12/F056		13-Sept-00		kg	F056	16 mg	PUA241	aluminum blister
	00I13/F057		14-Sep-00		kg	F057	24 mg	PUA241	aluminum blister
	00G25/F058		25-Jul-00			F058	Placebo		aluminum blister
	01A15/F058		18-Jan-01			F058	Placebo		aluminum blister
	00I29/F059		15-Sep-00			F059	1x4 mg tablet encapsulated	PUA152	aluminum blister
	00I30/F060		19-Sep-00			F060	2x4 mg tablet encapsulated	PUA152	aluminum blister
	00I30/F061		25-Sep-00			F061	3x4 mg tablet encapsulated	PUA152	aluminum blister
GAL-INT-21 (Clinical Safety Study)	01E03/F055		2-May-01		kg	F055	8 mg	PUA242	aluminum blister
	01E07/F056		7-May-01		kg	F056	16 mg	PUA242	aluminum blister
	01E21/F057		21-May-01		kg	F057	24 mg	PUA241/ PUA242	aluminum blister
	01E22/F057		15-May-01		kg	F057	24 mg	PUA241	aluminum blister

5.3 APPENDIX 3 STABILITY STUDY DATA

The following table summarizes the product information of the drug substance (DS) and drug product (DP) batches involved in the stability study. It is note worthy that 3 pellet batches of both [redacted] kg batch sizes were placed on stability using the lowest and highest capsule fill strengths. In addition, stability upon storage in both HDPE bottles and unit dose blister packaging is provided, (see Table 33 to Table 40).

Table 32 Summary of Batch Information of Batches Used in Stability Studies

Drug Product						Pellet			Drug Substance		
Batch No	F No.[a]	Strength (mg)	Mfg Date	Mfg Site	Batch Size[b] (# Capsules)	Batch No	Mfg Site	Batch Size (Kg)	Batch No	Mfg Site	Mfg Date
Registration batches											
00J10/F075	F075	8 mg	09Oct2000	[redacted]	[redacted]	00I19/F54	[redacted]	[redacted] kg	PUA241	[redacted]	03Jul2000
00J11/F075	F075	8 mg	09Oct2000			00I20/F54		kg	PUA242		03Jul2000
00J12/F075	F075	8 mg	09Oct2000			00I21/F54		kg	PUA151		14Oct1998
00J24/F077	F077	24 mg	11Oct2000			00I19/F54		kg	PUA241		03Jul2000
00J25/F077	F077	24 mg	11Oct2000			00I20/F54		kg	PUA242		03Jul2000
00J26/F077	F077	24 mg	11Oct2000			00I21/F54		kg	PUA151		14Oct1998
Concept of Manufacturing batch											
TS20401	F075	8 mg	04Dec2001			01H27/001		kg	PUA401		08Jun2001
TS20501	F075	8 mg	06Dec2001			01H29/002		kg	PUA411		08Jun2001
TS20601	F075	8 mg	06Dec2001			01H31/003		kg	PUA421		08Jun2001
TS21001	F077	24 mg	30Nov2001			01H27/001		kg	PUA401		08Jun2001
TS21101	F077	24 mg	02Dec2001			01H29/002		kg	PUA411		08Jun2001
TS21201	F077	24 mg	03Dec2001			01H31/003		kg	PUA421		08Jun2001

a) The Johnson and Johnson Pharmaceutical Research and Development Laboratories assigns Formula numbers ('F' from 'Formula') to specific pharmaceutical compositions.
b) Theoretical batch size

The following tables show all dissolution data for both [redacted] kg pilot and [redacted] kg commercial scale batches on stability. This data demonstrates the consistency and lack of variability of the dissolution data, thereby supporting the reviewer's conclusions regarding dissolution in spite of the sponsor's lack of using the most appropriate study designs and changing methodology.

Table 33 Stability Study Dissolution Results at 25°C/ H – 8 mg Caps– —g Batch - Manufactured at C J - Bottles

Study	Batch	Test Method	Storage (Months)	Dissolution (%) 1 hour(s)	4 hour(s)	8 hour(s)	12 hour(s)	r(s)	(s)	Content Mean	Assay
007246	00J10/F075 8 mg No Packaging	F/D/0923/01	C							99.6	F/A/2152/01
										99.8	
										99.5	
002248	00J10/F075 8 mg HDPE cap	F/D/0923/01								99.6	F/A/2152/01
										98.1	
										99.7	
										97.9	
										98.4	
										100.0	
										98.3	
002249	00J11/F075 8 mg HDPE cap	F/D/0923/01								98.3	F/A/2152/01
										98.8	
										98.4	
										98.5	
										98.1	
										99.2	
										98.7	
002251	00J12/F075 8 mg HDPE cap	F/D/0923/01								99.4	F/A/2152/01
										98.7	
										98.6	
										99.3	
										100.4	
										99.6	
										98.4	

Table 34 Stability Study Dissolution Results at 25°C/ H – 8 mg Caps– [redacted] kg Batch - Manufactured at [redacted] – Bottles

Study	Batch	Test Method	Storage (Months)	Dissolution (%) 1 hour(s)	4 hour(s)	8 hour(s)	12 hour(s)	Content Mean	Content Assay
A50043	TS20401 F075 8 mg HDPE Cap	F/D/0923/01	[redacted]					99.4	F/A/2152/01
								98.2	
								100.2	
								101.4	
A50046	TS20501 F075 8 mg HDPE Cap	F/D/0923/01						102.7	F/A/2152/01
								99.2	
								100.9	
								101.4	
A50050	TS20601 F075 8 mg HDPE Cap	F/D/0923/01						98.6	F/A/2152/01
								98.6	
								100.2	
								98.6	

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Table 35 Stability Study Dissolution Results at 25°C/ :H – 24 mg Caps– ⁻ xg Batch - Manufactured at C J · Bottles

Study	Batch	Test Method	Storage (Months)	Dissolution (%) 1 hour(s)	4 hour(s)	8 hour(s)	12 hour(s)	Content Mean	Assay
002257	00J24/F077 F077 24 mg HDPE caps	F/D/0925/01	C					100.7	F/A/2154/01
								98.6	
								98.3	
								99.3	
								100.0	
								99.7	
								98.3	
007259	00J25/F077 F077 24 mg No Packaging	F/D/0925/01						99.3	F/A/2154/01
								98.7	
								98.3	
002258	00J25/F077 F077 24 mg HDPE caps	F/D/0925/01						98.4	F/A/2154/01
								99.1	
								98.3	
								99.8	
								98.7	
								100.2	
								99.8	
002260	00J26/F077 F077 24 mg HDPE caps	F/D/0925/01						100.8	F/A/2154/01
								99.4	
								99.1	
								100.8	
								99.6	
								99.7	
								98.7	

Table 36 Stability Study Dissolution Results at 25°C/ – 24 mg Caps– [ ]g Batch - Manufactured at [ ]- Bottles

Study	Batch	Test Method	Storage (Months)	Dissolution (%) 1 hour(s)	4 hour(s)	8 hour(s)	12 hour(s)	Content Mean	Assay
A50059	TS21001 F077 24 mg HDPE caps	F/D/0925/01	[						F/A/2154/01
A50062	TS21101 F077 24 mg HDPE caps	F/D/0925/01							F/A/2154/01
A50064	TS21201 F077 24 mg HDPE caps	F/D/0925/01							F/A/2154/01

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Table 37 Stability Study Dissolution Results at 25°C – 8 mg Caps– [redacted] kg Batch - Manufactured at [redacted] - Blisters

Study	Batch	Test Method	Storage (Months)	Dissolution (%)				Content	
				1 hour(s)	4 hour(s)	8 hour(s)	12 hour(s)	Mean	Assay
A50010	00J10/F075 F075 8 mg Blister \	F/D/0923/01	[redacted]					98.8	F/A/2152/01
								100.1	
								100.5	
								100.2	
								98.9	
								99.0	
								99.1	
A50011	00J11/F075 F075 8 mg Blister \	F/D/0923/01						99.8	F/A/2152/01
								98.6	
								99.2	
								99.2	
								99.7	
								99.0	
								100.5	
A50012	00J12/F075 F075 8 mg Blister \	F/D/0923/01						99.9	F/A/2152/01
								99.5	
								98.1	
								99.4	
								99.9	
								98.2	
								98.1	

Table 38 Stability Study Dissolution Results at 25°C - 8 mg Caps- — kg Batch - Manufactured at [ ] - Blisters

Study	Batch	Test Method	Storage (Months)	Dissolution (%) 1 hour(s)	4 hour(s)	8 hour(s)	12 hour(s)	Content Mean	Assay
A50067	TS20401 F075 8 mg Blister \	F/D/0923/01	[					99.4	F/A/2152/01
								99.3	
								99.2	
								99.7	
A50068	TS20501 F075 8 mg Blister \	F/D/0923/01						102.7	F/A/2152/01
								98.5	
								100.1	
								98.1	
A50069	TS20601 F075 8 mg Blister \	F/D/0923/01						98.6	F/A/2152/01
								98.1	
								98.8	
							]	100.4	

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Table 39 Stability Study Dissolution Results at 25°C. – 24 mg Caps– kg Batch - Manufactured at [redacted] Blisters

Study	Batch	Test Method	Storage (Months)	Dissolution (%) 1 hour(s)	4 hour(s)	8 hour(s)	12 hour(s)	Content Mean	Assay
A50016	00J24/F077 F077 24 mg Blister	F/D/0925/01	[redacted]					98.9	F/A/2154/01
								98.5	
								101.3	
								99.2	
								99.6	
								99.1	
								98.7	
A50017	00J25/F077 F077 24 mg Blister	F/D/0925/01						98.7	F/A/2154/01
								99.1	
								98.7	
								99.1	
								98.9	
								98.8	
								98.4	
A50018	00J26/F077 F077 24 mg Blister	F/D/0925/01						99.6	F/A/2154/01
								99.1	
								98.9	
								99.9	
								100.0	
								99.0	
								98.4	

Table 40 Stability Study Dissolution Results at 25°C/ H – 24 mg Caps- — kg Batch - Manufactured at [ ] – Blisters

Study	Batch	Test Method	Storage (Months)	Dissolution (%) 1 hour(s)	4 hour(s)	8 hour(s)	12 hour(s)	Content Mean	Assay
A50073	TS21001 F077 24 mg Blister	F/D/0925/01	[					99.8	F/A/2154/01
								100.0	
								98.9	
								97.6	
A50074	TS21101 F077 24 mg Blister	F/D/0925/01						101.0	F/A/2154/01
								98.9	
								99.6	
								98.2	
A50075	TS21201 F077 24 mg Blister	F/D/0925/01						100.4	F/A/2154/01
								99.9	
								99.3	
								99.5	

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5.4 APPENDIX 4 FILING MEMO

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	21-615	**Brand Name**	Reminyl Extended Release Capsules
Related NDAs	21-169 21-224	**Generic Name**	Galantamine Hydrobromide Extended Release Capsules
OCPB Division (I, II, III)	I HFD-860	**Drug Class**	Anti-acetylcholinesterase (reversible, competitive inhibitor)
Medical Division	Neuropharmacology HFD-120	**Indication(s)**	Mild to Moderate Alzheimer's Disease
OCPB Reviewer	R. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.	**Dosage Form**	Modified Release Capsule
OCPB Team Leader	Raman Baweja, B.S. Pharm., Ph.D.	**Strengths:**	8 mg, 16 mg, 24 mg
Date of Submission	February 24, 2003	**Dosing Regimen**	qd
PDUFA Due Date	December 24, 2003	**Route of Administration**	Oral
Division Due Date	November 24, 2003	**Sponsor**	J&J / Janssen
Estimated Due Date of OCPB Review	November 10, 2003	**Priority Classification**	S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	5		There were 2 pilot studies that will not be reviewed. There is an additional pilot study that also examined the lowest strength of final TBM formulation. There was 1 pivotal BE study with highest strength TBM formulation. Plus an additional 1 BE study with TBM/CTF and the TBM formulation from a commercial batch (both highest strength)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		Only 1 study will be reviewed. There was 1 study with a pilot formulation and 1 study with highest strength of TBM formulation.
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References				
Total Number of Studies		8		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**April 30, 2003**	
Secondary reviewer Signature and Date	**April 30, 2003**	

CC: NDA 21-615
HFD-850 (P. Lee)
HFD-120 (GriffisM)
HFD-860 (KavanaghR, BawejaR, MehtaM, SahajwallaC)
CDR

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/s/

Ron Kavanagh
10/8/03 11:18:02 AM
BIOPHARMACEUTICS

Raman Baweja
10/8/03 12:56:13 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	21-615	**Brand Name**	Reminyl Extended Release Capsules
Related NDAs	21-169 21-224	**Generic Name**	Galantamine Hydrobromide Extended Release Capsules
OCPB Division (I, II, III)	I HFD-860	**Drug Class**	Anti-acetylcholinesterase (reversible, competitive inhibitor)
Medical Division	Neuropharmacology HFD-120	**Indication(s)**	Mild to Moderate Alzheimer's Disease
OCPB Reviewer	R. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.	**Dosage Form**	Modified Release Capsule
OCPB Team Leader	Raman Baweja, B.S. Pharm., Ph.D.	**Strengths:**	8 mg, 16 mg, 24 mg
Date of Submission	February 24, 2003	**Dosing Regimen**	qd
PDUFA Due Date	December 24, 2003	**Route of Administration**	Oral
Division Due Date	November 24, 2003	**Sponsor**	Jannsen
Estimated Due Date of OCPB Review	November 10, 2003	**Priority Classification**	S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
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Phase 2:				
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Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References				
Total Number of Studies		8		

Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				April 30, 2003
Secondary reviewer Signature and Date				April 30, 2003

CC: NDA 21-615
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/s/

Ron Kavanagh
4/30/03 04:06:13 PM
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Raman Baweja
4/30/03 04:23:09 PM
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