

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-615**

**Chemistry Review(s)**

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS  
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-615

CHEM.REVIEW # 2

REVIEW DATE: 02-AUG-04

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-FEB-03	25-FEB-03	28-FEB-03
Amendment	21-NOV-03	24-NOV-03	24-NOV-03

NAME & ADDRESS OF APPLICANT:

Johnson & Johnson  
1125 Trenton-Harbourton Rd  
Titusville, NJ 08560-0200

DRUG PRODUCT NAME

Proprietary:  
Nonproprietary/USAN:  
Code Name#:  
Chem.Type/Ther.Class:

Reminyl (galantamine hydrobromide) ER Capsules  
galantamine hydrobromide  
R113675  
Drugs for Memory/2013060

PHARMACOL.CATEGORY/INDICATION:

Mild to Moderate AD

DOSAGE FORM:

Extended Release Capsules

STRENGTHS:

8/16/24 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

XXXXX Rx \_\_\_\_\_ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(-)-[4aS-(4a $\alpha$ ,6 $\beta$ ,8aR\*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide

CAS Registration number : 1953-04-4

Molecular weight : 368.27 (287.36 + 80.91)

Molecular formula : C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>.HBr

SUPPORTING DOCUMENTS: IND 35,544, NDA 21-224, DMF

RELATED DOCUMENTS: none

REMARKS/COMMENTS: The overall recommendation by the OC was issued on 14-MAR-04 after delays caused by apparent mergers and reorganizations.

CONCLUSIONS & RECOMMENDATIONS: No outstanding CMC concerns. Recommend approval of NDA 21-615. Copy of EER attached.

cc:

Orig. NDA 21-615

HFD-120

HFD-120/WJRzeszotarski

HFD-120/MGriffis

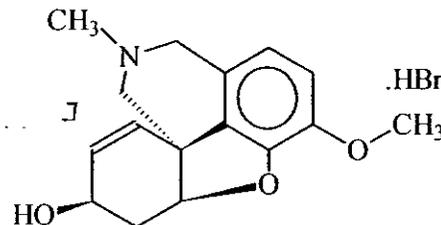
HFD-120/MEGuzewska

R/D Init by:MEG

/s/

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: E:\msword\N21615R.002.doc



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/s/

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Janusz Rzeszotarski  
8/2/04 11:36:44 AM  
CHEMIST

Maryla Guzewska  
8/2/04 12:27:20 PM  
CHEMIST



**NDA 21-615**

**Reminyl Extended Release Capsules**

**Johnson & Johnson**

**Chemistry Review  
W. Janusz Rzeszotarski, Ph.D.  
HFD-120**

Table of Contents

Table of Contents.....1

Chemistry Review Data Sheet.....2

The Chemistry Executive Summary.....5

I. Recommendations.....5

    A. Recommendations and Conclusions on Approvability.....5

    B. Recommendations on Phase IV (Post-Marketing) Commitments, Agreements,  
        and/or Risk Management Steps, if Approvable.....5

II. Summary of Chemistry Assessments.....5

    A. Description of the Drug Product and Drug Substance.....6

    B. Description of How the Drug Product is Intended to be Used.....6

    C. Basis for Approvability or Not Approvability.....6

III. Administrative.....6

Chemistry Assessment.....7

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### Chemistry Review Data Sheet

1. NDA # 21-615
2. REVIEW #: 1
3. REVIEW DATE: 23-OCT-2003/01-DEC-2003
4. REVIEWER: W. Janusz Rzeszotarski, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED: An amended submission.

Submission(s) Reviewed

Document Date

- |             |           |
|-------------|-----------|
| 7. Original | 24-FEB-03 |
| Amendment   | 23-NOV-03 |

8. NAME & ADDRESS OF APPLICANT:

Name: Johnson & Johnson  
Address: 1125 Trenton-Harbourton Rd  
Titusville, NJ 08560-0200

Representative: James H. Medley, Ph.D.  
Telephone: 609-730-3049

9. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary: Reminyl (galantamine hydrobromide) Extended Release Capsules
- b) Non-Proprietary: Galantamine Hydrobromide
- c) Code Name/# R113675
- d) Chem. Type/Submission Priority: 3S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of mild to moderate Alzheimer's Disease

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 8/16/24 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) NO

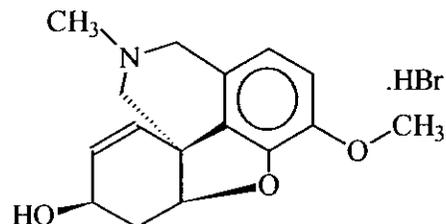
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(-)-[4aS-(4a $\alpha$ ,6 $\beta$ ,8aR\*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide

CAS Registration number : 1953-04-4

Molecular weight : 368.27 (287.36 + 80.91)

Molecular formula : C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>.HBr



16. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
7	II	J&J	Galantamine Hydrobromide Synthetic	3	Adequate	27-JAN-2003	API
	III			3	Adequate	23-OCT-2002	
	III			3	Adequate	27-SEP-2000	
	III			4	N/A	Not in EDQ	
	III			3	Adequate	19-JUL-02	
	III			3	Adequate	27-SEP-2002	
	III			3	Adequate	05-OCT-1993	
	IV			3	Adequate	07-JAN-2003	
	IV			3	Adequate	03-OCT-2002	
	III			3	Adequate	30-MAY-2003	
	III			3	Adequate	22-JUL-2002	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, inadequate, or N/A

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,703 AT 27-DEC-2000	Janssen – Controlled Release Capsules
IND	51,538 AT 06-SEP-1996	Janssen – Galantamine HBr Tablets
NDA	21-224 AP 22-JUN-2001	Janssen - Oral Solution for AD
NDA	21-169 AP 28-FEB-2001	Janssen - Tablets

**18. STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A		
EES	pending		OC
Pharm/Tox	N/A		
OCPB/DPE1	Acceptable	08-OCT-2003	Ron Kavanagh, Pharm.D.
Methods Validation	In preparation		
EA	Acceptable	23-OCT-2003	W.Janusz Rzeszotarski, Ph.D.
Microbiology	N/A		
DMETS	In review		

**The Chemistry Executive Summary**

**I. Recommendations**

**A. Recommendation and Conclusion on Approvability**

The submission represents the third formulation of galantamine hydrobromide. In difference to the previous NDAs 21-169 (tablets) and 21-224 (oral solution) this formulation permits once a day dosing, a substantial improvement for AD patient caregiver. The drug substance now used is of synthetic origin and is supported by DMF [ 1]. Regrettably the specifications different from the DMF-established for that API specifications were used throughout the document. The sponsor was requested on 27-OCT-03 to clarify the issue by submitting to this NDA the established acceptance specifications. The amendment of 23-NOV-03 clarified the issue but indicated that several batches of API were made out of drug substance not meeting the current specifications. Otherwise the purity profile and the stability of the drug product resemble that for the approved applications. Both, the drug substance and the drug product, are proven stable but the stability data for the final formulation supports expiration dating to 18 months only. From the CMC point of view this amended application is recommended as approvable subject to the EER recommendation (see the attached copy of EES and E-mails).

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

N/A

**II. Summary of Chemistry Assessments**

Galantamine hydrobromide, an inhibitor of acetylcholine esterase, is an approved drug substance for treatment of mild to moderate Alzheimer's Disease. The present application represents an extended release formulation facilitating the administration.

**A. Description of the Drug Product and Drug Substance**

**Drug Product.** The capsules of 8mg, 16 mg, and 24 mg strength consist, in dose proportional manner, of the tri-layer controlled release pellets. The controlled release pellets consist of [ ] sugar spheres coated with three layers: 1) a controlled release drug layer, 2) a rate controlling membrane and 3) an immediate release drug layer. The immediate release drug layer provides the initial drug level while the dissolution of rate controlling membrane provides for a controlled drug release over 24 hours. The controlled release pellets have a concentration of [ ] mg/g of galantamine hydrobromide equivalent to [ ] mg/g of galantamine free base. All components of the pellet (except for drug substance) are made of USP/NF or Ph. Eur. grade excipients. The components of the pellets are: a) [ ] Sugar Spheres NF; b) controlled release drug layer - galantamine hydrobromide and Coating [ ] made of Hypromellose [ ] USP and [ ] rate controlling membrane - Ethylcellulose [ ] USP, Hypromellose [ ] USP, and Diethyl Phthalate NF and d) immediate release drug layer - galantamine hydrobromide and Coating [ ] The solvents used in manufacturing of the pellets: [ ] are removed during the process. The Hard Gelatine Capsules of Sizes 4, 2 and 1 are made from BSE- free sources.

Before encapsulation the controlled release pellets may be shipped in [ ] [ ] When needed the extended release capsules may be shipped in [ ] [ ] The extended release capsules are packaged: a) 30 capsules [ ] [ ] HDPE white bottle with child resistant closure; b) 300 capsules in a [ ] [ ] HDPE white bottle with [ ] [ ] closure and c) [ ] [ ] Aluminum blisters.

The bottle configurations are made of high density polyethylene resin [ ] [ ] and manufactured by [ ] [ ] Blister packs are made of [ ] [ ] supplied by [ ] [ ] [ ] aluminum foil supplied by [ ] [ ]

The results of [ ] real time stability studies (A50016, A50017, A50018, (blisters) and 002257, 002258, 002260 (bottles) of the validation batches in similar to commercial packaging forms [ ] [ ] HDPE bottles) prove that the drug product is stable and support the 18 months expiration dating.

**Drug Substance.** Galantamine hydrobromide was initially manufactured from the galantamine extracts obtained from daffodils. With the increased demand the sponsor developed a synthetic method to manufacture the drug substance in a manner described in DMF [ ] [ ] The synthetic process introduced two new impurities absent in the API of botanical origin. These impurities [ ] [ ] have been qualified and approved by the clinical and pharmacological reviewers [ ] [ ] In variance to botanical source the [ ] [ ] the synthetic galantamine hydrobromide was set as: specified impurities [ ] [ ] and the [ ] [ ] In addition the [ ] [ ] was raised to ICH acceptable level [ ] [ ] ppm and the [ ] [ ] specification was added as [ ] [ ] ppm.

**B. Description of How the Drug Product is Intended to be Used**

Galantamine hydrochloride extended release capsules will be provided in three strengths of 8 mg, 16 mg and 24 mg in three packaging configurations. The standard room temperature storage is recommended and the expiration date of 18 months is justified.

**C. Basis for Approvability or Not-Approval Recommendation**

A stable formulation and a proven stability of API. The API and drug product specifications justified after ammnedment of 23-NOV-2003.

**III. Administrative**

Chemist: W. Janusz Rzeszotarski, Ph.D./01-DEC-2003

ChemistryTeamLeader/ Date: Maryla E. Guzewska, Ph.D.

Project Manager / Date: Melina Griffis, R.Ph

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**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS  
Review of Chemistry, Manufacturing, and Controls  
CHEM.REVIEW # 1**

**NDA #: 21-615**

**REVIEW DATE: 01-DEC-03**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-FEB-03	25-FEB-03	28-FEB-03
Amendment	23-NOV-03	23-NOV-03	23-NOV-03

**NAME & ADDRESS OF APPLICANT:**

Johnson & Johnson  
1125 Trenton-Harbourton Rd  
Titusville, NJ 08560-0200

**DRUG PRODUCT NAME**

**Proprietary:**

**Nonproprietary/USAN:**

**Code Name/#:**

**Chem.Type/Ther.Class:**

Reminyl (galantamine hydrobromide) ER Capsules  
galantamine hydrobromide  
R113675  
Drugs for Memory/2013060

**PHARMACOL.CATEGORY/INDICATION:**

Mild to Moderate AD

**DOSAGE FORM:**

Extended Release Capsules

**STRENGTHS:**

8/16/24 mg

**ROUTE OF ADMINISTRATION:**

Oral

**DISPENSED:**

XXXXX Rx \_\_\_\_\_ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

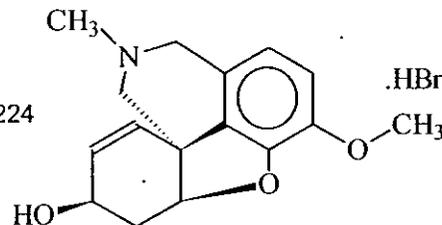
(-)-[4aS-(4α,6β,8aR\*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-

6-ol hydrobromide

CAS Registration number : 1953-04-4

Molecular weight : 368.27 (287.36 + 80.91)

Molecular formula : C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>.HBr



**SUPPORTING DOCUMENTS:** IND 35,544, NDA 21-169 (tablets) 21-224

(oral solution), DMF [ ] (synthetic galantamine hydrobromide).

**RELATED DOCUMENTS:** none

**REMARKS/COMMENTS:** Submitted in CTD format. The controlled release pellet technology is well accepted and documented (see salbutamol sulphate, amitriptyline, theophylline, verapamil and norverapamil, etc formulations) but should not be identified with the far more advanced [ ] Technology). In the above submission a tri-layer approach produces pellets consisting of [ ] sugar spheres coated with a controlled release drug layer, rate controlling membrane and immediate release drug layer. The capsules are dose proportional i.e the pellet formulation [ ] remains the same for all three strengths.

**CONCLUSIONS & RECOMMENDATIONS:** The reproducibility of manufacturing methods, the purity and stability of the product has been demonstrated. This issue of acceptance specifications for deug substance has been resolved. Recommend NDA 21-615, as amended, approvable with the 18 months shelf life at 25°C, subject to final EER.

cc:

Orig. NDA 21-615

HFD-120

HFD-120/WJRzeszotarski

HFD-120/MGriffis

HFD-120/MEGuzewska

R/D Init by:MEG

**W. Janusz Rzeszotarski, Ph.D., Chemist**

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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