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

SUBMISSION TYPE
ORIGINAL
Amendment

DOCUMENT DATE
24-FEB-03
21-NOV-03

CDER DATE
25-FEB-03
24-NOV-03

ASSIGNED DATE
28-FEB-03
24-NOV-03

NAME & ADDRESS OF APPLICANT:
Johnson & Johnson
1125 Trenton-Harbourton Rd
Titusville, NJ 08560-0200

DRUG PRODUCT NAME
Proprietary:

Nonproprietary/USAN:
galantamine hydrobromide

Code Name/#: R113675

Chem.Type/Ther.Class:
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_{17}H_{21}NO_{3}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

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: E:\msword\N21615R.002.doc
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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

Maryla Guzewska
8/2/04 12:27:20 PM
CHEMIST
Reminyl Extended Release Capsules

Johnson & Johnson

Chemistry Review
W. Janusz Rzeszotarski, Ph.D.
HFD-120
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Appears This Way
On Original
Chemistry Review Data Sheet

1. NDA # 21-615

2. REVIEW #: 1


4. REVIEWER: W. Janusz Rzeszotarski, Ph.D.

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
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6. SUBMISSION(S) BEING REVIEWED: An amended submission.

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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: X Rx  OTC
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) NO**

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

(-)-[4αS-(4αα,6β,8αR*)]-4α,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol hydrobromide  
CAS Registration number : 1953-04-4  
Molecular weight : 368.27 (287.36 + 80.91)  
Molecular formula : C_{17}H_{21}NO_{3}·HBr

16. **RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

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1 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”)

2 Adequate, inadequate, or N/A
B. Other Documents:

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<th>DOCUMENT</th>
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<td>IND</td>
<td>61,703 AT 27-DEC-2000</td>
<td>Janssen – Controlled Release Capsules</td>
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<td>IND</td>
<td>51,538 AT 06-SEP-1996</td>
<td>Janssen – Galantamine HBr Tablets</td>
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<td>21-224 AP 22-JUN-2001</td>
<td>Janssen - Oral Solution for AD</td>
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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:

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<td>W. Janusz Rzeszotarski, Ph.D.</td>
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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 E1. Regrettfully 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 8 mg, 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 Hypermellose and USP and rate controlling membrane - Ethyelcellulose USP, Hypermellose and 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 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. Blister packs are made of 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 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 impurities the synthetic galantamine hydrobromide was set as: specified 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**

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
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: Reminyl (galantamine hydrobromide) ER Capsules
Nonproprietary/USAN: galantamine hydrobromide
Code Name/#: R113675
Chem.Type/Ther.Class: 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-(4aα,6β,8αR*)]-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-
ef][2]benzazepine-6-ol hydrobromide
CAS Registration number: 1953-04-4
Molecular weight: 368.27 (287.36 + 80.91)
Molecular formula: C_{17}H_{21}NO_{3}\cdot HBr

SUPPORTING DOCUMENTS: IND 35,544, NDA 21-169 (tablets) 21-224
(oral solution), DMF \[\text{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 drug
substance has been resolved. Recommend NDA 21-615, as amended, approving 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

filename: E:\msword\N21615nr.002.doc
53 Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
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/s/

Martha Heimann
12/19/03 05:46:47 PM
CHEMIST