CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-169

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

NDA#: 21-169

CHEM.REVIEW # 3

REVIEW DATE: 30-OCT-00

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NAME & ADDRESS OF APPLICANT:

Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

DRUG PRODUCT NAME

Proprietary: Reminyl (galantamine hydrobromide) Tablets
Nonproprietary/USAN: Galantamine hydrobromide
Code Name#: 1S/Acetylcholine Esterase Inhibitor
Chem.Type/Ther.Class:

PHARMACOL.CATEGORY/INDICATION:
AD

DOSAGE FORM:
Tablets

STRENGTHS:
4 mg, 8 mg, 12 mg (eq to base)

ROUTE OF ADMINISTRATION:
Oral

DISPENSED:
	xxxx Rx OTC

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

(4aS,6R,8αS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuran[3a,3,2-e][2]benzodiazepin-6-ol hydrobromide

C₂₉H₂₈BrN₂O₄: Molecular Weight: 368.27;
CAS #: 1953-04-0 (hydrobromide); 357-70-0 (base)

SUPPORTING DOCUMENTS: DMF [galantamine HBr]

RELATED DOCUMENTS:

REMARKS/COMMENTS: Reply to IR Letter of 29-JUN-00 and to AE letter of 29-JUL-00. Most of the concerns addressed in the IR letter have been addressed and the DMF deficiencies corrected. It appears that USAN accepted Reminyl trademark as a catch-them-all name for both galantamine and galantamine hydrobromide. See the copy of E-mail attached. The sponsor agrees to use the name Reminyl only in conjunction with the galantamine hydrobromide. Facilities acceptable as of 21-JUL-00. Copy of EER attached.

CONCLUSIONS & RECOMMENDATIONS: Recommend the approval of NDA 21-169.

cc:
Orig. NDA 21-169
HFD-120
HFD-120/WJRzeszotarski
HFD-120/Fanari
HFD-120/MEGuzewska
R/D Init by: MEG

/s/ W. Janusz Rzeszotarski, Ph.D., Chemist
Redacted 8

pages of trade secret and/or confidential commercial information
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDAS: 21-169

CHEM.REVIEW #2

REVIEW DATE: 29-JUN-00

SUBMISSION TYPE
DOCUMENT DATE
CDER DATE
ASSIGNED DATE
ORIGINAL
25-MAY-00
26-MAY-00
26-MAY-00

NAME & ADDRESS OF APPLICANT:
Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

DRUG PRODUCT NAME
Proprietary:
Reminyl (galantamine hydrobromide) Tablets
Nonproprietary/USAN:
Galantamine hydrobromide
Code Name/Code:
1S/Acetylcholine Esterase Inhibitor
Chem.Type/Ther.Class:
AD

PHARMACOL.CATEGORY/INDICATION:
DOSAGE FORM:
Tablets
STRENGTHS:
4 mg, 8 mg, 12 mg (eq to base)
ROUTE OF ADMINISTRATION:
Oral
DISPENSED:
XXXXX Rx________ OTC

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

(4aS,6R,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-e][2]benzodiazepin-6-ol hydrobromide
C\textsubscript{17}H\textsubscript{23}BrNO\textsubscript{3}; Molecular Weight: 368.27;
CAS #: 1953-04-0 (hydrobromide); 357-70-0 (base)

SUPPORTING DOCUMENTS: DMF\(\textsubscript{galantamine HBr})

RELATED DOCUMENTS:

REMARKS/COMMENTS: Reply to IR Letter of 21-MAR-00. Most of the concerns addressed in the IR letter have been addressed except for the API and drug product specifications which have to be consolidated and edited to actual analytical findings in the batches supporting the clinical studies.

CONCLUSIONS & RECOMMENDATIONS: Recommend the NDA 21-169 approvable subject to the resolution of remaining specification issues and an acceptable EER. Draft IR letter attached. The most recent copy of EER attached and the E-mail exchanges pertinent to timely completion of inspections by the OC.

cc:
Orig. NDA 21-169
HFD-120
HFD-120/WJRzeszotarski
HFD-120/Fanari
HFD-120/MEGuzewskak
R/D Init by: MEG

W. Janusz Rzeszotarski, Ph.D., Chemist
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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-169
CHEM.REVIEW # 1
REVIEW DATE: 21-MAR-00

SUBMISSION TYPE
ORIGINAL

DOCUMENT DATE
29-SEP-99

CDER DATE
29-SEP-99

ASSIGNED DATE
04-OCT-99

NAME & ADDRESS OF APPLICANT:
Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

DRUG PRODUCT NAME
Proprietary:

Nonproprietary/USAN:
Galantamine hydrobromide

Code Name/#:

Chem.Type/Ther.Class:
1S/Acetocholine Esterase Inhibitor

PHARMACOL.CATEGORY/INDICATION:
AD

DOSAGE FORM:
Tablets

STRENGTHS:
4 mg, 8 mg, 12 mg (eq to base)

ROUTE OF ADMINISTRATION:
Oral

DISPENSED:
XXXXX Rx_________OTC

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

(4aS,6R,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]-benzodiazepin-6-ol hydrobromide

C_{17}H_{22}BrNO_3; Molecular Weight: 368.27;
CAS #: 1953-04-0 (hydrobromide); 357-70-0 (base)

SUPPORTING DOCUMENTS: DMF
[ ] galantamine HBr

RELATED DOCUMENTS:

REMARKS/COMMENTS: Galantamine is a tertiary alkaloid that has been isolated from the bulbs of the Caucassian snowdrop Galanthus woronii (Proskurina and Yakovleva, 1952), the common snowdrop Gananthus nivalis (Bolt, various species of Narcissus (Bolt et al., 1957) and other plant sources. The galantamine hydrobromide, used to make the tablets described in present application, is of plant origin, produced from the extract from the bulbs of Narcissus pseudonarcissus (daffodil) of the varieties "Carlton" and "Tee Follies". The sponsor amended the IND to provide for the synthetic galantamine HBr but has not included that source of API in the NDA submitted. All Reminyl tablet formulations have the same qualitative and dose-proportional quantitative tablet core composition. Size, color and embossing differentiate tablets of different strength from each other. The application does not provide the acceptance methods for the API, covered by the DMF[ ] and the MV is made impossible by creation of individual methods, in name, for each strength. Other deficiencies are also listed in the IR letter (see attached).

CONCLUSIONS & RECOMMENDATIONS: Fact that in the present form the DMF does not support the NDA 21-169, and the improper organization of MV documents makes MV impossible renders the NDA not-approvable. Draft IR letter attached. The most recent copy of EER attached.

cc:
Orig. NDA 21-169
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MMalandrucco
HFD-120/MEGuzewska
R/D Init by:MEG

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: E:\msword\n21169r.001.doc
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secret and/or

confidential

commercial

information
DMF REVIEW COVER FORM

DMF: DMF Type: II

Title: Galantamine Hydrobromide Drug Substance

1. CHEM REVIEW #  1   2. REVIEW DATE:  16-MAR-2000

3. ITEM REVIEWED

A. IDENTIFICATION

USAN 
Ingredient Dictionary name    applied for galantamine hydrobromide (USAN listing)
Name     Galantamin, Galanthine, Nivalin, Nivalina, Lycoremin,
Karatonon code R113675/073575
Chemical names ([4aS-(4αc,6R,8aS)] -4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide (USAN appl.)
4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide (Merck Index)
([4aS-(4αc,6β,8aR*)] -4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide (CA Service)

CAS number, if available  1953-04-0 (hydrobromide)  357-70-0 (base)

B. LOCATION IN DMF

Type of Submission Date of Submission Location of Information
Original

4. PREVIOUS DOCUMENTS

Type of Document Date of Document Description

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

REPRESENTATIVE or U.S. AGENT (if applicable):
NAME:
ADDRESS:

CONTACT PERSON’S
ADDRESS:
TELEPHONE NUMBER:

6. DMF REFERENCED FOR:

NDA ANDAAADAIND: NDA 21-169
PRIMARY DMF (as needed)
APPLICANT NAME: Janssen Research Foundation
LOA DATE: 29-SEP-99
DRUG PRODUCT NAME: REMINYL (galantamine) Tablets
DOSAGE FORM: Tablets
STRENGTH: 4 mg, 8 mg & 12 mg

CODE:XXX
ROUTE OF ADMINISTRATION: Oral

7. SUPPORTING DOCUMENTS: CODE: XXX

8. CURRENT STATUS OF DMF:
   DATE OF LAST UPDATE OF DMF: N/A
   DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:
   Janssen Pharmaceutica; 29-SEP-99

9. CONSULTS: None

10. COMMENTS: * and are neither supported by the batch analysis nor backed by the patient exposure during the clinical trials. Minor other deficiencies (see the Draft Deficiency Letter)

11. CONCLUSION: In its present form the DMF is deficient and does not support the NDA 21-169.

cc:
Original DMF
HFD-1ND/NDA # 21-169 Division File
HFD-120/Divison Director
HFD-120/MMalandrucco
HFD-120/MGuzewska
HFD-120/WJRzeszotarski

Drafted by: drafter's initials/date
Initialed by:
final:

DMF REVIEW

16 MAR 2000
Redacted 40

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commercial

information
**Application:** NDA 21169/000  
**Stamp:** 29-SEP-1999  
**Regulatory Due:** 28-FEB-2001  
**Applicant:** JANSSEN RES FDN  
11250 TRENTON HARBOURTON RD  
TITUSVILLE, NJ 085600200  
**Priority:** 1S  
**Org Code:** 120  
**Action Goal:**  
**District Goal:** 30-MAY-2000  
**Brand Name:** REMINYL(GALANTHAMINE)4MG/8MG/1  
2MG TABLET  
**Estab. Name:**  
**Generic Name:** GALANTHAMINE  
**Dosage Form:** (TABLET)  
**Strength:** 4 MG, 8 MG, 12 MG  
**Application Comment:** PRODUCT SPECIFIC INSPECTION (on 30-NOV-1999 by W. RZESZOTARSKI (HFD-120) 301-594-2850)  
**FDA Contacts:**  
M. PANARI (HFD-120) 301-594-5526, Project Manager  
W. RZESZOTARSKI (HFD-120) 301-594-2850, Review Chemist  
M. GUZEWSKA (HFD-120) 301-594-5571, Team Leader  

**Overall Recommendation:** ACCEPTABLE on 21-JUL-2000 by P. ALCOCK (HFD-324) 301-827-0062  
**Establishment:** 9614770  
JANSSEN CILAG SPA  
LATINA, IT  
**DMF No:**  
**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
**Profile:** TCM  
**OAI Status:** NONE  
**Estab. Comment:**  

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Adequate Firm Response  
Based on review of Firm's Response and FDA-483 - Investigator Recommendation has not been sent to HFD-322 or DEIO as of yet and could not be located. UF 7-29-00  
OC RECOMMENDATION 21-JUL-2000 ACCEPTABLE ALCOCKP DIRECTION RECOMMENDATION  
Based on review of FDA-483 and Firm's Response only - Review of EIR to follow upon receipt to HFD-322  

**Establishment:** 2650104  
JANSSEN ORTHO INC  
STATE RD 933 KM 0.1 MAMEY WARD  
GURABO, PR 00658  

**DMF No:**  
**Responsibilities:** FINISHED DOSAGE PACKAGER  
**Profile:** TCM  
**OAI Status:** NONE  
**Estab. Comment:**  

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Based on profile  

**Establishment:** 2242843  
JANSSEN PHARMACEUTICA INC
### Milestone Details

**DMF No:**

**Responsibilities:** FINISHED DOSAGE RELEASE TESTER

**Profile:** CTL

**OAI Status:** NONE

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**Establishment:** 9610034

JANSSEN PHARMACEUTICA NV
B-2440
GEEL, , BE

**DMF No:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Profile:** CSN

**OAI Status:** NONE

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Establishment:

DMF No: AADA:
Responsibilities:
Profile: TCM OAI Status: NONE
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PHI-DO CONDUCTED AN INSPECTION 9/99, CLASSED NAI.

OC RECOMMENDATION 29-DEC-1999 ACCEPTABLE EGASM DISTRICT RECOMMENDATION

Establishment:

DMF No: AADA:
Responsibilities:
Profile: TCM OAI Status: NONE
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APPEARS THIS WAY ON ORIGINAL
**ESTABLISHMENT EVALUATION REQUEST**

**DETAIL REPORT**

**Application:** NDA 21169/000  
**Stamp:** 29-SEP-1999  
**Regulatory Due:** 29-JUL-2000  
**Applicant:** JANSSEN RES FDN  
1125 TRENTON-HARBOURTON RD  
TITUSVILLE, NJ 085600200  
**Priority:** 1S  
**Org Code:** 120  

**Action Goal:**  
**District Goal:** 30-MAY-2000  
**Brand Name:** REMINYL (GALANTHAMINE) 4MG/8MG/1 2MG TABLET  
**Estab. Name:**  
**Generic Name:** GALANTHAMINE  
**Dosage Form:** (TABLET)  
**Strength:** 4 MG, 8 MG, 12 MG

**Application Comment:** PRODUCT SPECIFIC INSPECTION (on 30-NOV-1999 by W. RZESZOTARSKI (HFD-120) 301-594-2850)

**FDA Contacts:**  
M. FANARI (HFD-120) 301-594-2850, Project Manager  
W. RZESZOTARSKI (HFD-120) 301-594-2850, Review Chemist  
M. GUZEWKA (HFD-120) 301-594-5571, Team Leader

**Overall Recommendation:** ACCEPTABLE on 21-JUL-2000 by P. ALCOCK (HFD-324) 301-827-0062

**Establishment:** 9614770  
JANSSEN CILAG SPA  
LATINA, IT

**Responsibilities:** FINISHED DOSAGE MANUFACTURER

**Profile:** TCM  
**OAI Status:** NONE

**Milestone Name** | **Date** | **Req. Type** | **Insp. Date** | **Decision & Reason** | **Creator**
--- | --- | --- | --- | --- | ---
SUBMITTED TO OC | 30-NOV-1999 | | | | RZESZOTARS
SUBMITTED TO OC | 30-NOV-1999 | | | | RZESZOTARS
SUBMITTED TO DO | 01-DEC-1999 PS | | | | EGASM
ASSIGNED INSPECTION | '03-DEC-1999 PS | | | | EGASM
INSPECTION SCHEDULED | 20-JUN-2000 | | | | IRIVERA
INSPECTION PERFORMED | 21-JUL-2000 | | | | ALCOCKP
DO RECOMMENDATION | 21-JUL-2000 | | | | ACCEPTABLE ALCOCKP

**ADEQUATE FIRM RESPONSE**  
BASED ON REVIEW OF FIRM'S RESPONSE AND FDA-483 - INVESTIGATOR RECOMMENDATION HAS NOT BEEN SENT TO HFD-322 OR DEIO AS OF YET AND COULD NOT BE LOCATED. UF 7-29-00

**OC RECOMMENDATION** 21-JUL-2000  
**ACCEPTABLE** ALCOCKP  
**DISTRICT RECOMMENDATION**

**Based on Review of FDA-483 and FIRM'S RESPONSE ONLY - REVIEW OF EIR TO FOLLOW UPON RECEIPT TO HFD-322**

---

**Establishment:** 2242843  
JANSSEN PHARMACEUTICA INC  
1125 TRENTON HARBOURTON RD  
TITUSVILLE, NJ 08560

**DMF No:**  
**Responsibilities:** FINISHED DOSAGE RELEASE TESTER

**Profile:** CTL  
**OAI Status:** NONE

**Milestone Name** | **Date** | **Req. Type** | **Insp. Date** | **Decision & Reason** | **Creator**
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SUBMITTED TO OC | 30-NOV-1999 | | | | RZESZOTARS
SUBMITTED TO OC | 30-NOV-1999 | | | | RZESZOTARS
SUBMITTED TO DO | 01-DEC-1999 GMP | | ACCEPTABLE | | FERGUSONS
DO RECOMMENDATION | 01-FEB-2000 | | | | ACCEPTABLE RBRON4
OC RECOMMENDATION | 01-FEB-2000 | ACCEPTABLE | | | DAMBROGIOJ
### Establishment: 9610034

**JANSSEN PHARMACEUTICA NV**

**B-2440**

**GEEL, , BE**

#### DMF No: AADA:

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Profile:** CSN

**OAI Status:** NONE

#### Estab. Comment:

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### Establishment:

#### DMF No: AADA:

**Responsibilities:**

**Profile:** TCM

**OAI Status:** NONE

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### Establishment:

#### DMF No: AADA:

**Responsibilities:**

**Profile:** CEX

**OAI Status:** NONE

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OC RECOMMENDATION 22-JUN-2000

Establishment:

DMF No: AADA:
Responsibilities: CRU OAI Status: NONE
Profile: EGASM
Estab. Comment:

Milestone Name | Date       | Req. Type | Insp. Date | Decision & Reason | Creator
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SUBMITTED TO OC | 30-NOV-1999 |          |            |                  | RZESZOTARS|
SUBMITTED TO OC | 30-NOV-1999 |          |            |                  | RZESZOTARS|
SUBMITTED TO DO | 01-DEC-1999 | GMP      |            |                  | EGASM   |
ASSIGNED INSPECTION | 22-DEC-1999 | GMP      |            |                  | EGASM   |
INSPECTION SCHEDULED | 09-APR-2000 |          | 12-MAY-2000 |                  | IRIVERA |
INSPECTION PERFORMED | 15-MAY-2000 |          | 11-MAY-2000 |                  | EGASM   |
DO RECOMMENDATION | 18-JUL-2000 |          |            | ACCEPTABLE       | EGASM   |
OC RECOMMENDATION | 18-JUL-2000 |          |            | DISTRICT RECOMMENDATION | EGASM |

Establishment:

DMF No: AADA:
Responsibilities: TCM OAI Status: NONE
Profile: EGASM
Estab. Comment:

Milestone Name | Date       | Req. Type | Insp. Date | Decision & Reason | Creator
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SUBMITTED TO OC | 30-NOV-1999 |          |            |                  | RZESZOTARS|
SUBMITTED TO OC | 30-NOV-1999 |          |            |                  | RZESZOTARS|
SUBMITTED TO DO | 01-DEC-1999 | GMP      |            |                  | FERGUSONS|
DO RECOMMENDATION | 28-DEC-1999 |          |            | ACCEPTABLE       | DPAVANO |
PHI-DO CONDUCTED AN INSPECTION 9/99, CLASSED NAI.
OC RECOMMENDATION | 29-DEC-1999 |          |            | ACCEPTABLE       | EGASM   |
DISTRICT RECOMMENDATION |

Establishment:

DMF No: AADA:
Responsibilities: TCM OAI Status: NONE
Profile: EGASM
Estab. Comment: ESTABLISHMENT CHANGED NAME TO
EFF. 2/9/99; CPN AND LABELER CODE REMAINS THE SAME. (on 01-DEC-1999 by M. TORRES IRIZARRY (HFR-SE550) 787-729-
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