CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-224

Administrative Documents

PATENT AND EXCLUSIVITY INFORMATION

REMINYL® (galanthamine) Oral Solution – New Drug Application

Active Ingredient:	Galanthamine
Strength:	4 mg/ml
Dosage Form:	Solution
Route of Administration:	Oral

Patent and Exclusivity Information:

U.S. Patent Number:	4,663,318
Expiration Date:	January 15, 2006
Type of Patent:	Method of Use
Name of Patent Owner:	Synaptech, Inc. 17 Seacrest Drive Huntington, N.Y. 11743

The undersigned declares that Patent 4,663,318 covers the formulation, composition, and/or method of use of REMINYL® (galanthamine) Oral Solution. This product is the subject of this application for which approval is being sought.

Date: January 24, 2000

Mary A. Appollina

Mary A. Appollina
Attorney for Applicant
Registered Patent Attorney
Registration No. 34,087

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	021224	**Trade Name:**	REMINYL (GALANTAMINE) 4MG/ML ORAL SOLUTI
Supplement Number:	000	**Generic Name:**	GALANTAMINE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	FOR THE TREATMENT OF PATIENTS WITH ALZHEIMER'S DISEASE
Action Date:	2/3/00		

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Either BOF or EOF is True, or the current record has been deleted. Requested operation requires a current record.

/newpedsdev/Pedsview.asp, line 166

Pediatric Use Waiver

In accordance with 21 CFR 314.55(c)(2), we are hereby applying for a full waiver of the provision to provide pediatric use information for REMINYL® (galantamine) Oral Solution. The proposed indication for REMINYL® is the "treatment of mild to moderate dementia of the Alzheimer's type". As listed in the December 2, 1998 Federal Register Notice, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule" {[Page 66648]}, Alzheimer's disease is a disease for which a waiver will likely be granted due to the fact that the disease does not have sufficient significance in the pediatric population.

Chc LaPree

31 JANUARY 2000

Charles LaPree
Manager, Regulatory Affairs

Date

Debarment Certification

In accordance with the Generic Enforcement Act of 1992, we certify that Janssen Research Foundation did not and will not use in any capacity the services of any person or firm debarred under subsection (a) or (b) [section 306 (a) or (b) of the Federal Food, Drug, and Cosmetic Act] in connection with NDA 21-224 for REMINYL ® (galantamine) Oral Solution

We also hereby certify that flawed Intel Pentium computer chips were not used to perform any analyses included in NDA 21-224.

Janssen Research Foundation verifies that all trials conducted in the United States that are used to support NDA 21-224, were conducted in compliance with the Institutional Review Board regulations in 21 CFR Part 56 and the informed consent regulations in 21 CFR Part 50. Non-US protocols used to support the claims in this application were reviewed by independent Ethics Committees / Review Boards and these trials were performed in accordance with the declaration of Helsinki and its subsequent revisions.

Charles LaPree
Manager, Regulatory Affairs

31 January 2000
Date

Financial disclosure or certification statement

In compliance with 21 CFR 314.50 (k), Janssen Research Foundation is submitting this certification in support of the New Drug Application for REMINYL ® (galantamine) Oral Solution.

I certify that Janssen Research Foundation has not entered into any financial agreement with the clinical investigators listed in this application whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I further certify that no investigator was granted a proprietary interest in the product as defined in 21 CFR 54.2(c).

Please note that none of the clinical trials contained in this New Drug Application were ongoing as of February 2, 1999. Therefore in accordance with 63 FR72181, December 31, 1998, no information was collected retroactively from clinical investigators regarding significant equity interest or significant payments of other sorts as defined in 21 CFR 54.2(b) & (f), respectively.

Cle LaPree

Charles LaPree
Manager, Regulatory Affairs

31 JANUARY 2000

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: June 19, 2001
From: Armando Oliva, MD
To: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
Subject: Team Leader Memorandum for NDA 21-224, Reminyl Oral Solution

Janssen Pharmaceuticals requests approval of Reminyl Oral Solution for the treatment of mild to moderate dementia of the Alzheimer's type. We have already reviewed this application and sent the sponsor an approvable letter on 12/1/2000. In that letter, we informed Janssen that we could not approve the application for the oral solution at that time because approval relied on data contained in the Reminyl tablet application (NDA 21-169), and that application was still under review. We also asked the sponsor to incorporate our suggested changes to the proposed labeling.

The Agency approved the Reminyl tablet NDA on 2/28/01. The sponsor submitted its response to the approvable letter for the oral solution two months later on 4/26/01.

The sponsor is combining the labeling for the oral solution with that of the approved tablet labeling, resulting in one labeling for the two formulations. This is similar to the currently approved labeling for Maxalt (and other products) and should be acceptable. The proposed labeling is basically the approved Reminyl tablet labeling, with appropriate and minor modifications that are relevant to the oral solution. They plan to submit the new labeling to the tablet NDA as a CBE labeling supplement. I describe the proposed changes below.

- There is a description of the oral solution in the *Description* section
- The *Precautions* and *Dosage and Administration* sections now contain a new paragraph that directs the reader to instruct the caregiver on the proper use of the oral solution and to refers them to the instruction sheet.
- The *How Supplied* section contains additional information about the oral solution

The medical reviewer, Dr. Mani, describes these changes on page 4 of his review.

Our Division of Drug Marketing, Advertising, and Communication (DDMAC) reviewed the patient instruction sheet. They recommended changes that basically add clarity and simplifies the language used in the instructions which are intended to improve the comprehensibility of the material. I agree with these changes and we received the sponsor's concurrence with these changes on 6/19/01. The only difference between DDMAC's recommended changes and the sponsor's current version is that DDMAC suggested that the sponsor clarify the close-up of the pipette (figure 3b, page 2), but the

sponsor left it alone. I don't think this is a big issue and I accept the sponsor's version.

There are no outstanding chemistry, pre-clinical, or biopharm issues.

In summary, I believe the sponsor has adequately addressed the issues contained in the approvable letter. I recommend approval of the NDA.

/S/ 6/19/01

Armando Oliva, M.D.
Neurology Team Leader

MEMORANDUM

DATE: November 26, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-224

SUBJECT: Recommendation for Action on NDA 21-224, for the use of galantamine hydrobromide oral solution in patients with Alzheimer's Disease

NDA 21-224, for the use of galantamine hydrobromide oral solution in patients with Alzheimer's Disease was submitted by Janssen Pharmaceuticals on 1/31/00. An NDA for galantamine tablets was submitted by the sponsor on 9/29/99. That application contained the results of randomized controlled trials that supported the effectiveness of galantamine in patients with Alzheimer's Disease, as well as safety experience. That application was the subject of an Approvable letter dated 7/29/00. The sponsor submitted a response to that letter on 8/31/00, and is currently under review by the division.

The current application contained the results of a bioequivalence study (GAL-NED-5) which compared the steady state kinetics of a 12 mg BID dose of galantamine, given as both the tablet (the subject of the previously submitted NDA that is currently under review) and the oral solution. In addition, the sponsor has submitted CMC data for this formulation. The sponsor has referred to NDA 21-169 for the tablet for all other clinical and pre-clinical data.

The application has been reviewed by Dr. Ranjit Mani, medical reviewer (review dated 10/19/00), Dr. Sayed Al-Habet, Office of Clinical Pharmacology and Biopharmaceutics (review dated 5/19/00; this review was a joint review of the tablet and oral solution NDAs), Dr. Barry Rosloff, pharmacologist (review dated 10/17/00), and Dr. Janusz Rzeszotarski (reviews dated 8/14/00 and 10/30/00). All reviewers have concluded that the application is Approvable.

As noted by Dr. Mani, the oral solution has been demonstrated to be bioequivalent to the tablet. Because approval of this application is essentially entirely dependent upon approval of the tablet NDA, this application cannot be approved until that application is approved.

RECOMMENDATION

The sponsor should be sent the attached Approvable letter with accompanying labeling. The labeling is essentially the same as the label we included with the Approvable letter for NDA 21-169 for the tablet, save for some minor changes specifically related to the solution dosage form, as well as a patient information

sheet which describes for the care-giver how the dose is to be prepared (the solution is provided in a large multi-dose bottle and requires drawing up the solution into a pre-marked syringe which is provided) and administered.

[ ]

Russell Katz, M.D.

Cc:
NDA 21-224
HFD-120
HFD-120/Katz/Mani/Rosloff/Fitzgerald/Rzeszotarski/Guzewska/Fanari
HFD-860/Al-Habet

DELIVERED MAY 0 1 200

REQUEST FOR PROPRIETARY/ESTABLISHED NAME REVIEW

To: HFD-400; Room 15B03:Associate Director for Medication Error Prevention in the Office of Post-Marketing Drug Risk Assessment

From: HFD-120 - Division of Neuropharmacological Drug Products
Russell Katz, M.D., Director S 4/27/00

Date: April 28, 2000 # 5322

Application Status (IND/NDA/ANDA): NDA 21-224

Proposed Proprietary Name: Reminyl Oral Solution

Trademark registration status/Countries registered(if known): Registered but country unknown

Company tradename: Janssen

Other proprietary names by same firm for companion products: Pending NDA 21-169(Reminyl Tablets)Tentatively approved 10/22/1999. It is currently being re-evaluated for the 90-day prior approval request.

United States Adopted Name, dosage form, strength and dosing schedule:
Galantamine, Oral Solution, 4 mg/ml, dosed BID

Indication for use: For the treatment of mild to moderate dementia of the Alzheimer's type.

The user fee goal date for this application is December 3, 2000.

6/4/01

cc
NDA 21-224
HFD-120/Division File
HFD-120/CSO/Fanari

1 pages redacted from this section of the approval package consisted of draft labeling