

combination of subcutaneous injection of apomorphine and oral administration of levodopa/carbidopa. As part of the 13-week study, toxicokinetics of apomorphine were assessed both with and without levodopa/carbidopa treatment. Mylan is requested to submit these two studies also to OCPB for review.

- Since levodopa will be concomitantly used with apomorphine, the pharmacokinetic and pharmacodynamic drug-drug interaction study between apomorphine and levodopa in humans should be conducted. This study can be a Phase IV commitment.
- The Sponsor is requested to also submit the two studies, which evaluated the potential toxicity of a combination of subcutaneous injection of apomorphine and oral administration of levodopa/carbidopa, to OCPB for review.

CLINICAL

Efficacy

- DNDP requested that efficacy data collected relative to an "off" induced by withholding LD/CD treatment be analyzed separately from efficacy data collected from a spontaneously occurring "off." This request is particularly applicable to Study 202.
- In efficacy studies, provide a definition of aborted "off," present the % of aborted "off," and indicate the duration of aborted "off."

Safety

General

- The sponsor should
 - Integrate the safety experience across studies in the ISS and not merely summarize the experience in separate trials.
 - Present and analyze AEs/SAEs across subgroups according to age, gender, and race and discuss findings in the ISS.
 - Analyze drug-drug interactions in separate studies and across studies as an integrated assessment within the ISS.
 - Pay special attention to the analysis of orthostatic hypotension and related AEs/SAEs in separate trials and across studies as an integrated assessment within the ISS.

- Tabulate the total number of AEs/SAEs for potentially orthostatic hypotensive-related symptoms by dose received when AE/symptoms occurred or when orthostatic hypotension was observed

ECG Data

- The sponsor collected electrocardiographic data (desired by DNDP) in some studies using Holter monitors (3 lead) instead of standard 12 lead ECGs. In previous discussions with DNDP about collecting desired ECG data (especially for QTc), discussion had focused on collecting data with 12-lead ECGs. The sponsor did not discuss the acceptability of collecting desired data with 3 lead Holter monitors. Consequently, the sponsor must make a compelling, written argument why electrocardiographic data collected with 3 lead Holter monitors are valid for evaluating electrocardiographic effects (especially QTc) of —
- The sponsor should not mix or integrate electrocardiographic data collected with 3 lead Holter monitors with data collected using 12 lead ECGs. In addition, the sponsor should always specify whether electrocardiographic data presented were collected with 3 lead Holter monitors or 12 lead ECGs
- The sponsor noted that electrocardiographic data collected with 3 lead Holter monitors were interpreted by a cardiologist under blinded conditions
- The sponsor should
 - Specify the QT correction formula selected and validate that it is appropriate by showing that QTc does not vary with respect to heart rate (i.e. R-R interval)
 - Plot QTc vs plasma — level when available
 - Use pre-treatment ECG data as "baseline" if the data were obtained at ≥ 12 hours after the last — dose
 - Show changes of absolute electrocardiographic data (e.g. QTc) over time with respect to dose and study visit AND changes of electrocardiographic data (e.g. QTc) from "baseline" over time with respect to dose and study visit
 - Show maximal change of electrocardiographic data (e.g. QTc) over a treatment period with respect to dose and study visit
 - Present electrocardiographic data (e.g. QTc)
 - Present data on number of VPCs/hr, number of episodes of ventricular tachycardia (i.e. VT), and number of VT episodes per single treatment

- It would be desirable to see tabulated electrocardiographic data (e.g. QTc) plotted as a figure when multiple data points are available

Orthostatic VS data

- Orthostatic VS (pulse and blood pressure and specify positions studied) data should be tabulated and presented in a format as requested for electrocardiographic data (e.g. QTc)
- It would be desirable to see tabulated orthostatic VS data plotted as a figure when multiple data points are available
- The sponsor should
 - Define orthostatic hypotension
 - Tabulate the total number of AEs/SAEs for potentially orthostatic hypotensive-related symptoms by dose received when AE/symptoms occurred or when orthostatic hypotension was observed
 - Indicate how frequently orthostatic hypotension was symptomatic and asymptomatic
 - Provide a categorical breakdown of the frequency (# of patients and % of patients) of patients exhibiting any orthostatic hypotension according to your definition
 - Provide a categorical breakdown of the frequency (# of patients and % of patients) of patients exhibiting more severe orthostatic hypotension and provide a definition of more severe orthostatic hypotension
 - Tabulate the frequency of orthostatic VS data by mean daily dose of — and mean daily frequency of — dosing
 - Consider how to present and analyze various coding terms (e.g. light-headedness, dizziness, postural light-headedness or dizziness, vertigo, near-syncope, syncope, etc.) that might be associated with orthostatic hypotension
 - Indicate how frequently orthostatic hypotension was symptomatic and asymptomatic

NDA Format

- The sponsor confirmed that AE assessment of relationship to study drug will consist of multiple categories including not related, unlikely, possibly, probably, or definitely related to study drug

DNDP asked the sponsor to

- Provide normal, reference laboratory ranges for all laboratory values
- Provide tabulations of all abnormal laboratory values and all clinically significant (defined as a specified more severe abnormality) abnormal laboratory values
- Flag all abnormal laboratory values in patient listings as high (H) or low (L) It would be acceptable also to flag all clinically significant abnormal laboratory values (e.g. VH or VL)
- Provide a table of contents for tables, figures, and final study reports including titles and page location
- Provide all clinical protocols and amendments and specify in a table of contents their title and page location
- Tabulate (e.g. Table 3.3.1.d) the frequency of specific AEs/SAEs and AEs/SAEs by organ systems relative to mean dose. Provide a further breakdown of these specific AEs/SAEs and AEs/SAEs by organ systems relative to 1) duration of dosing, AND 2) number of treatment days, AND 3) frequency of mean daily dose
- Show the frequency (i.e. # of patients and % of patients) that a specific AE/SAE occurs in a population and a further breakdown of recurrence in individual patients
- Provide a further breakdown of all AE/SAE tables with respect to age, gender, and race

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Russell Katz

2/22/02 03 38 46 PM



PO Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

September 17, 2002

Russell G Katz, M D , Director
Division of Neuropharmacologic Drug Products, HFD 120
Central Document Room (Room #4-2833)
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

**RE Apomorphine Hydrochloride Injection, 10 mg/mL
NDA #21-264**

Dear Dr Katz

Reference is made to the New Drug Application (NDA) identified above for Apomorphine Hydrochloride Injection, 10 mg/mL that was submitted by Mylan Pharmaceuticals on April 17, 2000 and to the Agency's June 16, 2000 letter notifying Mylan of the Agency's decision to Refuse to File this application. Reference is also made to the Agency's correspondence dated June 27, 2001 designating Apomorphine Hydrochloride Injection as a fast track product.

Subsequent to the Agency's Refuse to File decision, Mylan/Bertek met with the Agency on July 25, 2000 (Informal Conference), September 14, 2000 (telephone conference), and January 10, 2002 (Pre-NDA Meeting) to discuss the requirements necessary to re-submit the application. During the September 14, 2000 telephone conference, the Agency indicated that a rolling review for the application was appropriate. The details of the rolling submissions were further discussed and defined in the January 10, 2002 Pre-NDA Meeting.

On May 6, 2002, Bertek initiated the submission of this rolling NDA with the re-submission of the Nonclinical Pharmacology and Toxicology Section (Section 5, Volumes 2 1-2 20) The Chemistry, Manufacturing and Controls Section (Section 4, Volumes 3 1-3 11) was re-submitted on June 14, 2002. The Human Pharmacokinetics and Bioavailability Section (Section 6 Volumes 4 1-4 16) was re-submitted on July 3 2002. The purpose of this submission is to provide the remainder of the application including the resubmission of Index to the Application (Section 1), Labeling Section (Section 2), Summary Section (Section 3), Clinical Data Section (Section 8), Statistical

Data Section (Section 10), Data Listings Section (Section 11) and Case Report Forms Section (Section 12) To the best of Bertek's knowledge, this submission along the three previous submissions constitutes a complete New Drug Application for the use of apomorphine hydrochloride injection 10 mg/mL in the rescue treatment of "off episodes" associated with Parkinson's disease

Pursuant to the Agency's guidance entitled "*Guidance for Industry Fast Track Drug Development Programs – Designation, Development, and Application Review*" (FDA, Procedural 9, September 1998) Bertek is requesting a priority review for this application Apomorphine Hydrochloride Injection for the proposed indication was granted Fast Track Designation on June 27, 2001 The use of apomorphine in the rescue treatment of "off episodes" provides a significant improvement compared to marketed products in the treatment of a serious disease While not directly life-threatening, *wearing off* and *on/off fluctuations* adversely impacts the activities of daily living resulting in significant recurring disability Currently, there are no approved products to acutely treat these events

As noted on the previous page, the original NDA was submitted by Mylan Pharmaceuticals Bertek Pharmaceuticals and Mylan Pharmaceuticals are both wholly owned subsidiaries of Mylan Laboratories Bertek is Mylan's marketing division for branded products and will be marketing the referenced product upon approval of the application Accordingly, this application is being re-submitted by Bertek Pharmaceuticals Mylan and Bertek are used interchangeably throughout the application

This application is covered by a user fee exclusion Apomorphine Hydrochloride Injection qualifies for Orphan Exception under section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act On April 22, 1993, an Orphan Drug Designation — was granted [] for apomorphine hydrochloride in the treatment of the on-off fluctuations associated with late stage Parkinson's disease On January 14, 1999, this Orphan Drug Designation was transferred to Mylan Pharmaceuticals Inc , Morgantown, WV A copy of the User Fee Cover Sheet Form (FDA 3397) is attached

Based on the Orphan Drug Designation for the referenced product and in accordance to 21 CFR 316.31, Bertek believes that, upon approval of this application, we will be entitled to 7 years of marketing exclusivity from the date of such approval during which FDA will not approve another sponsor's marketing application for the same drug

In accordance with 21 CFR 314.50(j), Mylan is claiming exclusivity as provided for in 21 CFR 314.108(b)(2), Mylan believes that upon approval of this application we will be entitled to five years exclusivity during which no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the Act for a drug product that contains the same active moiety that is in apomorphine hydrochloride injection To the best of Mylan's knowledge, a drug has not been previously approved under section 505(b) of the Act that contains any active moiety in the drug Apomorphine Hydrochloride Injection, 10 mg/mL

Pursuant to 21 CFR 314.55 (c), Mylan is requesting a full waiver of the requirement for pediatric use information. Apomorphine Hydrochloride Injection, 10 mg/mL for the rescue treatment of "off episodes" associated with Parkinson's disease does not represent a meaningful therapeutic benefit over existing treatment for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

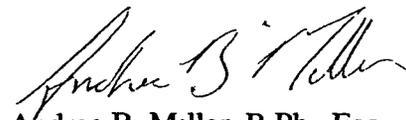
It should be noted that the application was formatted pursuant to 21 CFR 314.50. The attached Statement of Organization provides an overview of the format, indexing and pagination schemes used throughout this submission of the application and summarizes the organization of the previous submissions. The following Table of Contents detail the documentation submitted in support of this application.

Bertek Pharmaceuticals Inc. considers the information in this application to be confidential and proprietary. We request that no information from the application be disclosed to third parties without first obtaining written consent from Bertek.

Ten additional desk copies of NDA Volume 1 which contains the application index, product labeling, and application summary, has been forwarded to Teresa Wheelous, Senior Regulatory Management Officer.

All correspondence regarding this application should be directed to the attention of the undersigned at Bertek Pharmaceuticals Inc., P O Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6869 and/or facsimile number (304) 285-6407.

Sincerely,



Andrea B. Miller, R Ph , Esq
Director
Regulatory Affairs

Enclosures

MEMORANDUM OF TELEPHONE CONVERSATION
NDA # 21-264

Drug — (Apomorphine) Injection
Sponsor Mylan
Date September 14, 2000

Conversation Between

Agency

Dr R Katz – Division Director
Dr L Kapcala - Medical Reviewer
Dr J Feeney – Team Leader
Ms T Wheelous – Project Manager

Mylan Pharmaceuticals Attendees & Titles

Dr J O'Donnell – Exec VP, Research	Dr T Clark – Medical Director
Mr F Sisto – VP, Regulatory Affairs	Dr P Bottini – Exec Director, Clinical Research
Dr J Owen – Assist Director, PK	Andrea Miller, Esq – Assoc Director, Reg Affairs
Dr P McGrath – Director, Clinical Research	Dr M Huang – Pharmacokinetics Director

Purpose To inform Mylan of (1) the Agency's decision regarding the total number needed for an acceptable safety database, (2) the possibility of an early efficacy review, and (3) comments regarding study protocol #401

Discussion

Clinical Safety Database

- The valid safety database is extraordinarily small in size even for an Orphan designated product. The ICH guidelines recommend a database of 1500 total, 600 for up to 6 months and a minimum of 100 for one year.
- Whereas Mylan has proposed a total safety database of 400 patients, the Agency has decided that the minimally acceptable safety database is a total of 500 unique patients, 300 for 6 months, and 100 for one year.

Rolling Review

- An early efficacy review is appropriate and will be conducted as part of a rolling review.
- A rolling review will allow for Mylan to submit parts of the NDA, as they become available over a period of time. However, the review clock starts upon the submission of the last piece of information. The bulk of the safety data should be submitted early since an adequate review of the data will require a substantial amount of time.
- There is no absolute obligation to review the application prior to the submission of the last part of the NDA, but it would be beneficial to both the sponsor and the division to initiate the review prior to receipt of the last piece of information.
- The timing of all submissions should be relatively close together. The exact timing of the submissions can be discussed at a later date.

Protocols #401 and #302

Addition of New Clinical Pharmacology Study

- The current design of the new proposed trial does not study — in patients naive to — but studies, — only in patients already on drug for at least 3 months. It is necessary to include — naive patients in order to adequately characterize adverse events, orthostatic hypotension in particular
- Inclusion of a clinical pharmacology study of the following design is suggested in an effort to better characterize orthostatic hypotension
 - Enroll 50 patients naive to — and randomize 25 to drug and 25 to placebo. Then maintain this portion of the trial for 2 weeks while obtaining frequent ECG and blood pressure monitoring immediately before drug and at various times after drug administration on days 1, 8, and 15. It may also be necessary to prolong this intensive safety monitoring if a longer period (e.g. perhaps up to 4 weeks) is required to titrate patients to the highest doses and the sponsor desires labeling at the highest doses
 - At the end of the 2-week period the placebo patients would crossover to drug treatment. This group of 50 patients would then join the larger open label trial with periodic monitoring at 1 month and 4 months
- ECG and blood pressure monitoring for orthostatic (supine and standing blood pressure and pulse) hypotension should be conducted at baseline, week 1, and week 2 for the new clinical pharmacology study. The sponsor could also have the option of collecting additional data via automated ambulatory home blood pressure monitoring devices (but home health visits are not necessary) along with diary recordings of activity during the 2-week period
- Monitoring for all new patients in the open label trial should be conducted at an in office visit with the initial dosing (day 1) and with dosing at month one and month four. In office visits are desired to capture safety data of patients with regard to dosing
- Ideally, orthostatic VS monitoring with dosing should be conducted at day 1, month 1 and month 4 in all patients in the open label trial APO 401. However, in lieu of everyone coming in for an in office monitoring, it would be acceptable to negotiate a specific number of patients required to participate in the in office monitoring visits. The sponsor should also negotiate the specific number of patients required to have ECGs performed with dosing in the open label study
- Mylan would prefer to monitor 100% of the patients who have symptoms of orthostatic hypotension. It was noted, however, that symptoms of orthostatic hypotension may not necessarily be sensitive for illustrating all significant orthostatic hypotension. Systematic collection of orthostatic VS relative to dosing would better characterize the prevalence and severity of the potential for — induced orthostatic hypotension. Such information would be important especially for labeling

- Information gathered from patients who experience symptoms of orthostatic hypotension as well as from patients who have measurable orthostatic hypotension without symptoms would be more beneficial from the public health perspective
- Mylan asked if specific design of the new protocol (study APO302) and amendments to study APO401 could be developed in consultation with DNDP. The sponsor was told that this plan was acceptable

Need Additional High-Dose Data

- The high-dose portion _____ of the proposed dosage regimen _____ mg subcutaneous dose repeated up to a maximum of _____ daily has not been sufficiently studied to be permitted in labeling. If the high dose portion is desired in labeling, the sponsor should study this portion of the dose range for efficacy and safety
- Since patients are titrated to an individualized patient dose, and only a few patients will need the high-dose of _____ Mylan would rather not force high doses in patients who do not require it

Labeling for repeat dosing in the event of ineffective response

- It was pointed out that it was not apparent that the sponsor had collected sufficient data to address labeling of safety or efficacy of repeat _____ dosing in the event of an ineffective response to a dose

COMT Inhibitors

- Only a very small number of patients in _____ trials are also taking COMT inhibitors
- The concomitant use of _____ and COMT inhibitors, which reduce the total "off" time, should be adequately studied. It was recommended that the sponsor try to recruit patients into the new clinical pharmacology study who are already maximally treated with COMT inhibitors and continue to have break through "off" periods

ACTION ITEMS

- 1 Mylan will revise the ongoing protocol (study APO 401) and develop a new protocol (study APO 302) to include the elements discussed
- 2 Further discussions are needed to establish the exact timing of the NDA parts for a rolling review
- 3 If all new patients to be enrolled in the open label trial are not to participate in office monitoring of orthostatic VS and ECGs with respect to dosing at day 1, month one, and month four, then negotiation is needed to establish an acceptable number of patients who should be monitored for the desired safety parameters

NDA 21-264
Page 5

cc Orig NDA 21-264
 HFD-120
 /Katz
 /Feeney
 /Kapcala
 /Wheelous

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Draft September 15, 2000 / 9/25/00

TELECON

/s/

Teresa Wheelous
3/12/01 10 27 37 AM
CSO

Russell Katz
3/15/01 08 21 29 AM
MEDICAL OFFICER

MEETING MINUTES

DATE July 25, 2000
DRUG NAME 21-264 — (apomorphine hydrochloride) Injection
SPONSOR Mylan Pharmaceuticals Inc
TYPE OF MEETING Informal Meeting after Refusal to File Letter

ATTENDEES

Attendees & Titles

R Temple – Office Director	Dr R Katz – Division Director
L Kapcala – Medical Reviewer	Dr H Startzman – Orphan Drugs Reviewer
J McCormick – Orphan Drugs Director	Dr J Feeney – Group Leader
G Fitzgerald – Pharmacology Team Leader	
r L Freed – Pharmacology Reviewer	Dr J Whitley – Orphan Drugs Medical Reviewer
Jr S Yan – Biometrics Reviewer	Ms T Wheelous – Project Manager

Mylan Pharmaceuticals Attendees & Titles

Dr J O'Donnell – Exec V P Research	Dr T Clark – Medical Director
Mr F Sisto – V P , Regulatory Affairs	Dr P Bottini – Exec Director, Clinical Research
Dr J Owen – Assist Director PK	Mr R Moldin – C O O , President
Andrea Miller, Esq – Assoc Director Reg Affairs	
Dr P McGrath – Director, Clinical Research	
Dr M Huang – Pharmacokinetics Director	—— Neurology Consultant
—— – Consultant	—— Technical Consultant
J Akhurst – Medical Services Mngr	

MEETING OBJECTIVES

Discuss the June 16, 2000, refuse to file letter and obtain clarification on the deficiency points as detailed in this Agency letter

DISCUSSION POINTS

I Fast Track Desired

- Mylan was denied fast track designation under IND 52,844, however, Mylan believes that — qualifies for a fast track review and that fast track designation would best meet their needs
- Mylan believes that a fast track designation would have prevented a refusal to file and would provide the opportunity for a rolling review
- The proposed — claim for acute use in "off" periods is stated to be different from the claim of recently approved Parkinson's drugs. While these newer anti-Parkinson's drugs show a reduction in total "off" time, they are not labeled for acute use, as — is proposed to be. This difference is the grounds on which the fast track request is made

- Even with fast track designation or a priority status the review clock will not start until all of the data have been submitted

2 Inadequate Safety Database

- Patient exposure in the safety data base is very small (approximately 92 patients treated for various periods of time up to 10 weeks and followed prospectively) compared to the ordinary requirements of 1,500 total patient exposures, 300 – 600 patient exposures for 6 months, and 100 patient exposures for 1 year
- The sponsor proposed a patient exposure safety database of at least 400 patients for whom there would be adequate data derived from prospectively following patients forward in time at or above the proposed dose and with the proposed route of administration. This minimal number of 400 would consist of 100 patients followed for 1 year, 200 – 300 patients followed for 6 months, and approximately 92 patients who had participated in controlled trials and had been followed prospectively for some period. In addition, there would be some reliance on the safety experience described in the literature
- The Middlesex cohort data, from a retrospective study, is not presented well or characterized adequately to support the proposed labeling claims. These data are very heterogeneous, and complicated frequently by concomitant use of domperidone, a drug which is not approved in the U.S. and which is used to block peripheral actions (especially nausea, and orthostatic hypotension) of apomorphine. The database as submitted is not reviewable. For example, the adverse event orthostatic hypotension is not clearly or comprehensively reported
- If the Middlesex cohort is not permitted then the total safety base will be around 400, while 500 – 600 is preferred. Dr. Temple and the division will decide the exact number of patient exposures considered adequate for safety and the acceptability of the Middlesex data. The Division will contact Mylan with the Agency's decision

3 Protocol 401

- This protocol should be revised to monitor for orthostatic hypotension and ECG changes. Monitoring blood pressure and pulse for orthostatic changes around the time of drug administration will allow for better adverse event characterization in labeling
- The proposed dosing regimen is for a single subcutaneous dose to be given up to two or three doses per episode. This dosing regimen should be clearly documented in the protocol
- The initial titration period is utilized to establish each patient's individual dose. Since doses will vary in a range of up to 10 mg, there may be only a small amount of patient experience at the high end of the dose range. The amount of data available

at the different doses will limit the dosing recommended in labeling

- Additional pharmacokinetic parameters should be incorporated into the protocol to provide the required PK data Mylan plans to provide reports on in vitro PK studies in October 2000
- Mylan would like the Agency's comments on this protocol

4 **C**

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5 Efficacy Package

- Mylan would like a priority review and wonders if a review of the efficacy data prior to the safety review would expedite the total review time
- The Division will discuss and determine if a separate but early efficacy review will be performed

6 Preclinical Reports

- Final preclinical reports will be available in October 2000

ACTION ITEMS

- 1 Division will contact Mylan about the Agency's decision regarding an acceptable safety database number and the acceptability of the Middlesex cohort data
- 2 The Division will inform Mylan whether or not an early efficacy review will be performed
- 3 The Division will relay comments to Mylan regarding protocol 401

Signature, minutes preparer

Concurrence Chair

cc
NDA 21-264

NDA 21-264

4

HFD-120

HFD-120/Katz

/Feeney

/Kapcala

/Fitzgerald

/Freed

/Wheelous

HFD-860/Fetterly / Baweja

HFD-710/Yan / Jin

HF-35/ McCormick / Startzman

HFD-101/Temple

Draft August 14, 2000 / 8/29/00 & 11/1/00& 11/30/00 & 12/6/00

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INFormalMEETING MINUTES

/s/

Russell Katz

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Wheelous

NDA 21-264

JUN 16 2000

Mylan Pharmaceuticals Inc
Attention Frank R Sisto, V P Regulatory Affairs
781 Chestnut Ridge Road
P O Box 4310
Morgantown, WV 26504-4310

Dear Mr Sisto

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following

Name of Drug Product	Apomorphine hydrochloride 10 mg/ml Injection
Trade	—
Date of Application	April 17, 2000
Date of Receipt	April 18, 2000
Our Reference Number	NDA 21-264

We have given your application a preliminary review, and we find it is not sufficiently complete to merit review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Pharmacology / Toxicology



Clinical

I Inadequate Safety Database

The safety database consists of only a very small cohort of patients followed in a prospective manner with contemporaneously recorded adverse event (AE) data. Additionally, we acknowledge that you have submitted information from a cohort of patients from the Middlesex Hospital and reports of experience with apomorphine from the medical literature. Each of these groups is addressed below, along with their limitations. At the pre-NDA meeting on December 10, 1999, you were told that the Agency might accept an NDA for this product that did not contain prospective safety data from the full complement of patients described in the International Conference on Harmonization Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (i.e., a total of 1500 patients, with 300-600 treated for at least 6 months and 100 patients treated for at least 1 year), especially since this product has been given Orphan Product designation, but you were asked to propose an alternate number that might be acceptable. You did not propose such an alternative in any subsequent discussions. In this regard, the total prospectively followed cohort that is included in your application is far short of any reasonable number needed to adequately characterize the safety of your product.

- A Prospective Cohort** As far as we can determine, no more than 92 subjects were treated prospectively and followed for the occurrence of adverse events. Of these, 16 were treated for one day, so that only 76 patients contributed more than 1 day of safety data. Only approximately 14 patients were treated for at least 10 weeks. This number is clearly inadequate to establish the safety of this product. It is important to note several points relevant to our judgment in this matter:

While we acknowledge that your product has been designated an Orphan Product, by your own estimation there may be as many as — patients who would be eligible to receive this treatment if it were to be approved with the indication that you propose. An NDA for a treatment for a condition with this prevalence requires considerably more safety experience than you have submitted.

Further, while you assert that the patients enrolled in your trials have failed to respond to available treatments, you have not provided evidence that they are, in fact, fundamentally different than the patients enrolled in the development programs for other recently approved anti-Parkinson's therapies. In these other applications, safety databases of the size required by the ICH guidelines were included.

Finally, you refer, in your submission of 6/8/00, to several statements made by Agency personnel that you believe support your current submission

First, you state that the Office of Orphan Products suggested the option of a rolling submission. A rolling submission is a feature of an application that is submitted under the Fast Track provisions of the Food and Drug Administration Modernization Act (FDAMA), a designation that you have not requested. Drugs reviewed under these provisions will ordinarily also be reviewed as priority drugs. Even if the application were to be reviewed under these provisions, the review need not necessarily begin (and the review clock will not start) until all portions of the application have been submitted.

You also state that in the December 10, 1999 meeting, Dr. Temple suggested that, if the application were not to be submitted as a priority review application, you could "submit the NDA with the available data and then amend the application with the outstanding study reports at a later date." Our minutes do not include any such statements from Dr. Temple or any other Agency staff member from the December 10, 1999 meeting. However, our minutes of your June 23, 1999 phone call with Dr. Temple and Ms. Carter do state that Dr. Temple did say that you could submit the NDA before you had all the data from the "study in England." However, this was not intended to mean that the application could be submitted with a clearly inadequate safety database. We refer you to the ICH guidelines which states that data on patients treated through 12 months should be submitted "as soon as available and prior to approval." It was this sort of long-term data to which Dr. Temple referred. His statement was not intended to imply that the NDA could be submitted with an otherwise inadequate safety database.

- B Middlesex Hospital Cohort** Although this was a retrospective study, you believe that all patients (n=188) treated at this institution over time (13 years) have been included and their safety experience fully captured and described. Although there is no way to prove that all patients treated with apomorphine at this center are included in this report, we believe this may be a reasonable assumption. However, it is difficult to accept that all adverse event data were systematically collected over time on these patients without loss during treatment and follow-up.

In the treatment of advanced Parkinson's Disease, the distinction between treatment-related adverse events and the natural history of the underlying treated disease is not always clear. Significant adverse events could easily be attributed to the disease or concurrent medications and not recorded. Beyond that, there is no way to verify the accuracy of the

record review performed. The single neurologist who performed the review was unblinded and could unintentionally have brought his/her own biases to the recorded adverse events. For these reasons, we cannot be certain that all relevant adverse event data have been submitted.

In addition, your submission appears to contain contradictory statements regarding the methodology used to validate this database. Specifically, you state that Britannia Pharmaceuticals verified the data entry into CRFs performed by Dr. —. However, you then state that industrial sponsors were not permitted to view confidential patient records. Please clarify how the data entered into CRFs were validated if patient records were not permitted to be seen.

We have these other specific concerns with the Middlesex data:

- The experience from this retrospective review is extremely heterogeneous and combines data from patients treated with various routes/methods (SQ injection, SQ infusion, combined SQ injection and infusion, intranasal) of administration of apomorphine, often does not have dosage information associated with the particular route or method of administration, and is frequently confounded by the concomitant use of domperidone (a dopaminergic antagonist acting mainly peripherally to diminish pharmacological side effects) which is not approved in the U.S. Therefore, it is possible that much of this data is not relevant to an assessment of the product you wish to market. In any event, the data have not been analyzed in a manner that would permit a review of that portion of the safety experience that is relevant to the way — would be used (acute SQ injections) in the U.S.
- While there is one presentation of data (Table 16.2.7.1) for 35 patients who apparently were treated with only intermittent injections, only the number of AEs for given organ systems is presented, individual AEs are not tabulated. In addition, this is true for the entire cohort of 188 patients.
- It is not clear if dose/duration data are known for these 35 patients whose use would seem to reflect the manner in which — would be used in the U.S.
- There are 29 patients (including 13 deaths) for whom charts and CRFs are not available (Listing 14.3.2) for review.
- CRFs for patients who died (vol. 33, 16.3.1, 60 total, 47 available and 13 unavailable), and for patients who discontinued treatment with apomorphine because of adverse events (section 16.3.3, total 28) are not contained in the NDA.

- Data were not collected from patients who were given apomorphine for diagnostic purposes but who did not begin receiving “regular” apomorphine treatment. It is not clear what this means. We are concerned that these patients may have declined further treatment with apomorphine because of AEs experienced from this “diagnostic” use.
- When there were laboratory data from 6-12 month intervals, apparently only the latest data were collected for presentation. Thus all available data were not collected and presented.
- An analysis of cutaneous effects of SQ apomorphine was based upon a survey of 49 patients. It is not clear upon what basis the 49 patients were selected for this subgroup analysis.

C Literature Reports Description of the safety experience in the medical literature has the same deficiencies as those offered above for the Middlesex data. Although you have compiled information from 121 publications involving apomorphine administration to 2019 patients, this experience is heterogeneous (e.g., various doses, durations, route/method of administration-SQ injection, SQ infusion, intravenous, sublingual, oral, intranasal, transdermal, intramuscular, rectal-of apomorphine, and concomitant domperidone usage) in nature and it is not obvious that much of it is relevant to your proposed use of —. Conceivably, some utility might be derived from a careful review of these publications to compile dose/duration safety data for treatment involving intermittent injections of apomorphine in the absence of concomitant domperidone use. If such subgroup analyses were performed, a description of how the data were compiled should be contained within the NDA. Of critical concern, however, is the fact that in these publications, as in the Middlesex experience, there is no assurance that there was complete prospective adverse event ascertainment.

II Concurrent Domperidone

The serious adverse events that can occur with — include nausea, vomiting, drowsiness, hallucinations, orthostatic hypotension, and syncope. Concurrent domperidone has the potential to alter this profile, but domperidone is not an approved drug product in this country. Therefore, the safety data collected in patients on the combination domperidone- — may not support the use of — alone.

III Inadequate Presentation or Analysis of the Data Collected

In the ISS, you did not integrate the safety experience across studies but essentially summarized or reviewed the experience from individual studies and summarized the published literature

You did not summarize or analyze the number of patients who were treated and followed for AEs prospectively in the studies APO 202, 301/S-001, NIH, 101 with respect to dose/duration considerations

It does not appear that you have performed the required (age, gender, race) subgroup analyses or other appropriate subgroup analyses which would be of interest. Subgroup analyses relative to effectiveness and safety data are required for age, gender and race (CFR 314.50). Although you have performed subgroup analyses relative to age or gender for effectiveness data in some trials, this has not been done in all trials nor has there been a pooled analysis of all effectiveness data in the ISE. There do not appear to be the required subgroup analyses for adverse events and safety data for age, gender, and race in the individual trials or of pooled data from these trials in the ISS. It would also be of interest to perform separate subgroup analyses regarding effectiveness and safety data with respect to concomitant use of domperidone, and apomorphine dosing interval, as well as an assessment of the impact of anti-emetic treatment other than domperidone relative to safety data.

You have not analyzed drug-drug interactions across studies in the ISS. Although there is some discussion about special populations in the ISS, this discussion focuses on the published literature and is not derived from data in your studies.

It had been noted at the Pre-NDA meeting (12/10/99) that adequate documentation of orthostatic hypotension should be provided. However, you did not provide a comprehensive presentation of the frequency or severity of orthostatic hypotension with SQ injections in individual studies nor is there a comprehensive discussion of related issues in the ISS. At the Pre-NDA meeting, there was discussion about whether a test dose of apomorphine might be used to assess the risk of orthostatic hypotension, so that those with a significant response might be excluded from intermittent apomorphine injections. Orthostatic VS (blood pressure, pulse) were not collected in 2 trials (APO 202, 301). In one study (APO202), AEs presumably related to hypotension/orthostatic hypotension are subsumed under the terms dizziness/postural dizziness which occurred in 20% of patients, but there is no tabulation of the total number of episodes for this specific AE, how frequently it was posturally related, and therefore there can be no useful discussion about this AE which seems likely to be related to orthostatic hypotension. More importantly, as noted above, not only

were orthostatic VS data not collected, but VS data (which were collected) were not assessed with a temporal relationship to dosing of apomorphine

Although orthostatic blood pressure changes were measured in study APO101, there is no substantive discussion of this important drug effect in the study report

In study APO101 in which dizziness/postural dizziness occurred in 24% of patients, the study reports (original and re-analysis) and publication resulting from the study did not provide an accurate presentation of information contained in the CRFs. We will describe our findings on this point in some detail, as it is an example of a serious deficiency which might be expected to have occurred for other adverse events as well

According to both study reports, three patients (#s 14, 49, 50) withdrew from the trial because of hypotension but there were no blood pressure/heart rate data for two patients who withdrew from the study "because of unacceptable symptoms of hypotension". However, additional important, pertinent, information, which is available in the CRFs, was not presented. Patient # 14 had one episode of orthostatic hypotension during the testing period and at least 4 episodes of presumably orthostatic hypotension (all symptomatic including one characterized as near fainting) during the titration period after 1.6 or 2 mg of apomorphine. In the publication it was noted that blood pressure readings pre-dosing were 125/80 while supine and 110/70 while standing and fell to 110/70 while supine and to 90/65 while standing after 2 mg. However, this recount of data differs from the original report which notes that blood pressure (positions unspecified) was reduced from 125/85 to 110/65. In addition, examination of the CRFs for this patient revealed additional blood pressure measurements at a later date which showed more severe orthostatic hypotension in which supine (110/85) and standing (100/70) blood pressures decreased to 100/70 (supine) and to 80/50 (standing) (without a pulse change-80) at 15 minutes after 2 mg of apomorphine. Despite these results, the study reports did not interpret patient # 14's blood pressure changes as orthostatic hypotension because it is explicitly noted in both that "No orthostatic hypotension was observed". Patient # 49 dropped out of the study for symptoms (dizzy, sweating) probably related to orthostatic hypotension on day 2 during dopaminergic responsiveness testing. However, it is not possible to read the CRF description of the AE because the photocopy is too light and the fields where blood pressure/pulse readings are to be recorded are crossed out (except for supine and standing blood pressure/pulse results pre-drug). It is noted below the cross-out, "not saved because of side effects". Does this mean VS upon standing were obtained but not recorded or that they were not obtained? A third patient discontinued from the trial for orthostatic hypotension with nausea, profuse sweating, and fainting (duration not specified) after standing up after test dose 2. Examination of the CRF for this patient revealed results on test day 2 which showed that baseline blood pressure-pulse was 140/90-92 while supine and 130/80-108 upon standing and changed to 130/90-112 while supine and to 90/unmeasurable-120 upon standing at 15 minutes after test dose 1.

After an interval of at least 120 minutes, baseline blood pressure-pulse was 130/90-88 while supine and 130/80-108 upon standing and changed to 120/80-92 while supine and to < 80/unobtainable-without pulse obtainable upon standing at 15 minutes after test dose 2. For this case, the medical term faint was coded as syncope in an adverse event listing (Appendix 31) but there does not appear to be any mention of syncope in an AE table, nor is there a description or discussion of syncope or near syncope in the study reports or publication. Furthermore, there do not appear to be any accompanying narratives for these dropouts. In the re-analysis study report, under sections 12.3.2 and 12.3.3 narratives and analysis and discussion of deaths, other serious adverse events, and certain other significant adverse events, it is noted "Not applicable." It would seem that attention to orthostatic hypotension would be worthy of narrative descriptions and discussion particularly considering that this AE was the most frequent cause for study discontinuation for 3 of 8 drop-outs and that this AE may represent one of the most serious and significant AEs limiting the use of apomorphine in patients. Of note, symptomatic orthostatic hypotension occurred at relatively low doses of apomorphine, and it was not clear if these 3 patients were on domperidone, and if so, if their dosing regimen differed from those who did not seem to exhibit significant orthostatic hypotension.

It should further be noted that there is no tabulation of total number of AEs experienced by patients in study APO101 as opposed to tabulation of the number (i.e. frequency) of patients who experienced an AE (Table 16) in a particular phase of the trial. It is also possible that a significant number of the patients (i.e. 8) with at least one AE (and possibly more) characterized as "dizzy" (some of which were noted to be orthostatic and were coded as "dizzy" or "dizziness" or "vertigo" in Appendix 31-AE listing) may have experienced orthostatic hypotension. These data were presented in Table 16. Two patients (#s 14, 49) who discontinued the study because of orthostatic hypotension were noted to have an AE coded as dizziness. In Study APO202 which did not assess blood pressures for orthostatic hypotension, dizziness/postural dizziness was observed in 20% of patients. It is suspected that this AE likely reflects orthostatic hypotension. Thus, the prevalence of orthostatic hypotension may be significantly higher than seems apparent based upon data as presented in the NDA and might be found to be more frequent and more severe in U.S. patients who would not be taking concomitant domperidone to avoid or diminish the risk of orthostatic hypotension as were many patients for whom data are presented within the NDA. Based upon this somewhat in-depth review of this one particular issue, concern is raised as to the comprehensive nature, quality, and reliability of safety information presented in this study and possibly in other studies which were not subjected to a more careful review.

In APONIH study, VS including supine and standing blood pressures were supposedly monitored at 1 hour after each dose during the dose response phase (study report section 9.5.1.2) but Tables 12.5.A, B, and C did not tabulate blood pressure changes relative to orthostatic changes and there does not appear to

be any discussion of orthostatic changes relative to acute dosing. The report (section 12.5) notes that "There were no significant difference between treatments with respect to vital sign data"

In study 101, there are listings (Appendices 22-24) for clinical biochemistry and hematology results and urinalyses along with notations for which are abnormal and a reference to a normal range. However, there are no systematic analyses of abnormal results. In section 12.4.2 of the re-analysis of the original study report, it is noted that "Some values were unsystematically outside the normal range. But none of those values were clinically significant." This is a recapitulation of the study report. Because there is no tabulation of abnormal results and thus no analyses, it is difficult to understand how one could necessarily come to that conclusion.

IV Financial Disclosure Statements

There are no financial disclosure statements completed by investigators at one of the sites in one pivotal trial (APO202)

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application.

To file this application over FDA's protest, you must avail yourself of this informal conference.

**APPEARS THIS WAY
ON ORIGINAL**

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions, call Ms. Teresa Wheelous, Regulatory Project Manager, at (301) 594-2850.

Sincerely Yours



6/16/00

Russell Katz, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Evaluation I
Center for Drug Evaluation and
Research

CC

Archival NDA 21-624

HFD-120/division file

HFD-120/Wheelous

HFD-120/Katz

/Kapcala

/Fitzgerald

/Freed

/Guzewska

/Christodoulou

HFD-860/Baweja/Zhao

HFD-710/Jin/He

HFD-094/DDMS

DISTRICT OFFICE

Drafted May 24, 2000

Final INITIALS/DATE

Filename c:\wheelous\nda\ — ackrtfltr doc

ACKNOWLEDGE (AC) / REFUSAL TO FILE (RF)

38

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

Wheelous

AUG - 1 2000

NDA 21-264

Page 1

**MEMORANDUM OF TELEPHONE CONVERSATION
NDA # 21-264**

Drug — (Apomorphine) Injection

Sponsor Mylan

Date June 16, 2000

Conversation Between

Agency

Dr R Katz – Division Director

Dr L Kapcala - Medical Reviewer

Ms T Wheelous – Project Manager

Sponsor

Dr J O'Donnell – Exec VP, Research

P Bottini, Pharm D – Clinical Research

Dr M Huang – Exec Director

Dr J Owens – Assist Director, PK

Andrea Miller- Regulatory Affairs

Purpose To discuss the status of the — application regarding the acceptability for filing

Discussion

During an earlier conversation between Dr O'Donnell and Dr Katz, the general reasons for the Division's decision to refuse to file the application were discussed. As stated in that conversation, there are two areas of deficiency in the application. Specifically the deficient areas are the lack of the full preclinical requirements ordinarily required to constitute a complete application and the size and presentation of the clinical safety database.

Clinical Database

- The valid safety database is extraordinarily small in size even for an Orphan designated product. The ICH guidelines recommend a database of 1500 total, 600 for up to 6 months and a minimum of 100 for one year. There are approximately 90 patients that have been adequately followed forward in time for the intended population, at the intended dose and route of administration.
- For example, the Middlesex data submitted is from patients that were given doses and routes of administration different than the proposed doses and routes of administration. Some doses were not reported.
- The literature data submitted has the same problem in presentation as the Middlesex data (lack of consistency between the intended and the studied doses and routes of administration).
- Based upon a search of the adverse event, orthostasis, there appear to be discrepancies between the study reports and the presentations in the case report forms. The study reports as presented are incomplete.
- An additional factor that confuses the data presentation from all sources is the use of domperidone, an anti-emetic and peripheral dopaminergic antagonist, which is unapproved for use in the U.S.

- Mylan believes that the proposed indication, L

3 Parkinson's disease, meets an unmet need and should qualify for a reduction in the number of patients ordinarily required to support safety. The justification (evidence) needed to support the difference in claim from recently approved Parkinson drugs (capones) have not been provided. The patient population enrolled in the studies appear to be a similar patient population to that studied in recently approved Parkinson drugs which also decrease "off" time

- The exact number needed to satisfy the safety database requirements is greater than the current number submitted in the application plus 100 patients enrolled in an ongoing open label study. This open label study will collect data from these 100 patients followed prospectively for 6 months
- A total of 100 patients with 6-month data is insufficient, however, data from 500 patients prospectively followed forward in time for 6-months at the intended dose and route of administration would be good. Additionally, the case report forms should be complete

Rolling Review

- The idea of conducting a "rolling review", which is associated with a fast track review / designation was raised. Dr. Katz noted that fast track designation was not formally requested at the time of the NDA submission. Fast track designation is necessary for "rolling review" consideration
- Mylan recalls that fast track designation was requested under the IND, however, a letter denying fast track designation issued in June 1999
- However, the review clock starts upon the submission of the last piece of information. The bulk of the safety data should be submitted initially including data from a large number of patients followed for at least 6 months

Filing Over Protest

- Mylan suggested that they would appeal the Division's decision to refuse to file the current application

- Dr Katz explained that the only "appeal" option is to file over protest. The application would then be reviewed as is without the possibility of amending the application, and that based upon the content of the current application the division would recommend that a Not Approvable letter be sent.

Mylan requested that the Division provide comments on protocol 401

ACTION ITEMS

- 1 A copy of the refuse-to-file (RTF) letter will be faxed to Mylan today
- 2 When available the Division will provide comments to Mylan on protocol 401
- 3 Mylan will request an informal meeting to discuss the RTF issues addressed in the letter

/S/

Teresa Wheelous, RPh

cc Orig NDA 21-264
HFD-120

/Katz
/Kapcala
/Wheelous

1/1/00
+ 7/28/00

C:\wheelous\NDA — rftel.doc
Draft July 17, 2000 / July 28, 2000
Refuse-to-file TELECON

MODE = MEMORY TRANSMISSION

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END=AUG-01 14 34

FILE NO = 158

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FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
 (HFD-120)
 5600 FISHERS LANE
 ROCKVILLE, MARYLAND 20857
 FAX (301) 594-2859

Telecopier Cover Sheet

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DATE August 1, 2000
TIME 3 00 PM
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FAX # (304) 285-6407
FROM Teresa Wheelous, R Ph
 Senior Regulatory Management Officer

Total number of pages, including cover page 4
 If you do not receive all pages or have any problems with receiving call (301) 594 2850
MESSAGE

Frank
 This is a 4 page fax containing the Division's telecon minutes of our June 16 2000 discussion regarding the filing status of _____

FDA/MYLAN TELEPHONE CONFERENCE
Division of Neuropharmacologic Drug Products (DNNDP)
June 16, 2000

MINUTES

PARTICIPANTS

FDA Russell G Katz, M D , Division Director
Leonard Kapcala, M D , Medical Reviewer
Teresa Wheelous, R.Ph , Project Manager

MYLAN John P O'Donnell, Ph D , Executive Vice President Research & Quality Control
Peter Bruce Bottini, Pharm D, Executive Director, Clinical Research
Mei-Ying Huang, Ph D , Executive Director, Pharmacokinetics
Joel Owens, Ph D , Assistant Director, Pharmacokinetics
Andrea B Miller, Esq, Associate Director, Regulatory Affairs

MEETING PURPOSE

Mylan requested the telephone conference with the Division to discuss the discrepancies between Mylan's and the Division's minutes from the December 10, 2000 Pre-NDA meeting and the impact on the filing status of Mylan's New Drug Application (NDA) for Apomorphine Hydrochloride Injection

DISCUSSION

Refuse to File Decision

- Dr Katz indicated that Mylan's NDA for apomorphine was not acceptable for filing for two main reasons Pre-Clinical and Clinical Safety Database
- The Division is requiring a complete toxicology package
- The Division found the clinical safety database insufficient both in respect to size and presentation
- According to the Division's review, the safety database only contains data on 90 patients who were prospectively studied The vast majority of the 90 patients only received apomorphine for a short time
- Although apomorphine is an Orphan Drug, the Division stated that a database of 90 patients lacks robustness and is too small to assess the safety of the product
- The Division rejected the Middlesex data as primary safety data Even if they accepted that all adverse events data had been captured for all patients treated at Middlesex (which they do not accept), the Division had trouble interpreting the data due to lack of homogeneity The Middlesex Database had data from

multiple routes of administration, doses different than that proposed in the United States (or doses not identified) and concomitant use of domperidone

- The Division had the same criticism about the literature data. They can not confirm that all AE's were captured and the data presented is derived from multiple routes of administration and multiple/unknown doses
- The Division is requiring a safety database containing prospectively followed adverse event data in a patient population receiving apomorphine that is representative of both the route of administration and dose that is proposed in the NDA
- The Division also noted that review of the AE of orthostatic hypotension was inadequate. The Division noted instances of potential orthostatic hypotension/dizziness provided in the case report forms that were not described in the study report
- The Division also was concerned about the concomitant use of domperidone in the Middlesex Review. They believe that domperidone may mask certain adverse events that may occur in the United States and domperidone is not a drug which is approved for use in the United States

Efficacy Data.

- Mylan asked the Division of its current view of the efficacy data. Dr. Katz noted that the efficacy data has not been fully reviewed. However, the studies needed to demonstrate efficacy were provided in the NDA and the results presented by Mylan seemed to be impressive, BUT the Division could not comment until a full review was completed.

Proposed Indication.

- Mylan requested the Agency's feedback on the proposed indication. Dr. Katz indicated that the proposed indication was a valid indication. The Agency would request some changes in the wording of the indication during the NDA review.

Required Safety Database.

- The Division indicated that they would be willing to negotiate the required safety database with Mylan. Mylan should propose an alternate number. It may not be necessary to have the full ICH complement. Mylan indicated that the open label study (APO401) was currently ongoing with approximately 130 patients.

MEETING MINUTES

MEETING DATE	December 10, 1999
IND & DRUG NAME	52,844 Mylan Apomorphine Hydrochloride Injection
SPONSOR	Mylan Pharmaceuticals Inc
TYPE OF MEETING	Pre – NDA

ATTENDEES

FDA Attendees & Titles

Dr R Temple – Office Director	Dr R Katz – Acting Division Director
Dr L Kapcala – Medical Reviewer	Dr H Startzman – Orphan Drugs Division
Dr J McCormick – Orphan Drugs Director	
Dr V Tammara – Biopharmaceutics Team Leader, Acting	
Dr I Mahmood – Biopharmaceutics Reviewer	
Dr B Rosloff – Acting, Pharmacology Team Leader	
Dr L Freed – Pharmacology Reviewer	Dr K Jin – Biometrics Team Leader
Dr S Yan – Biometrics Reviewer	Ms T Wheelous – Project Manager

Mylan Pharmaceuticals Attendees & Titles

Dr J O'Donnell – Exec V P , Research	Dr T Clark – Medical Director
Mr F Sisto – V P , Regulatory Affairs	Dr P Bottini – Exec Director, Clinical Research
Dr J Owen – Assist Director, PK	
Andrea Miller, Esq – Assoc Director, Reg Affairs	
	Consultant Neurologist

MEETING OBJECTIVES

Discuss the (1) content and format of a new NDA submitted for _____
_____ Parkinson's Disease (PD) and (2) expedited review
requirements for a novel indication _____

DISCUSSION POINTS

I Proposed Labeling

Nomenclature

▸ The name, _____ will be submitted for review by the Labeling Nomenclature
Committee

Indication

▸ The proposed indication is _____

▸ This product will be used as an adjunct in patients currently being treated with
single or combination PD drugs, but are still experiencing periods of "off" The
intent of this product is to allow this group of PD patients to resume activities of
daily living when they experience severe periods of "off"

Adverse Events (AEs)

- The latency to "on" is faster for — than for levodopa, however, the adverse events (AEs) that occur with — are more serious than levodopa AEs. AEs that can lead to hospitalization are nausea, vomiting, drowsiness, neuropsychiatric events (e.g., hallucinations), orthostatic hypotension, dizziness, and syncope.
- It may be possible to predict the risk of orthostatic hypotension by assessing the one-hour response to —.
- Therefore, labeling may contain compensatory measures for addressing these serious AEs by recommending that — not be used in patients who experience acute orthostatic hypotension with — or in patients that experience hallucinations with —. As for patients who experience nausea, the use of an antiemetic will be suggested.

Dosage

- The proposed dosage will be individual dose to be determined by dose titration between — to a maximum of — as needed for reversal of individual "off" events. The maximum dose of — is based upon clinical trial data, although the U.K. marketed product recommends a maximum dose of 100 mg/day.

II Expedited Review RequestCriteria

- Mylan believes that — meets a compelling clinical need, that — provides dramatic efficacy, and that the benefits outweigh the risks, and therefore, should be granted expedited review.
- Priority criterion (expedited review) does not demand that the disease be serious, but rather that there be a clear advantage over currently available products. Since direct evidence from a controlled trial using a head-to-head comparison between — and other PD drugs has not been provided, it is unknown whether or not — offers a clear advantage over other PD products.

Reduction in Latency as Advantage

- While — may decrease the latency to "on" this effect may be true of other PD drugs as well. Based on product labeling of some of the newer PD products, a reduction in "off" time has been shown.
- Mylan believes that the patients participating in the controlled trials have been fully optimized on other PD drug treatments, including the newer dopamine agonists that report a reduction in "off time", and that the adjunctive use of subcutaneous apomorphine hydrochloride offers this patient group an additional reduction in "off" times, acutely.

- Mylan should make the case with supporting evidence that the shortening of the "off" episodes
- Mylan should show that these patients' PD treatments had been maximized and that there was no opportunity for additional benefit of additional PD therapy as currently recommended

III Drug Metabolism and Interaction

Drug Metabolism

- Drug metabolism and interaction data have not been provided and are currently not available. These data are elements that are required for filing and NDA.
- Metabolic data are especially important in specific populations (e.g., renally impaired population) that may require dose adjustments due to differences in metabolism and/or excretion.
- Mylan plans to submit literature references in support of the clinical pharmacokinetic section. The adequacy of these references is not clear.
- The literature summary of animal studies is limited.
- Since toxicity studies are ongoing, Mylan could attempt to obtain the outstanding data from these studies, especially animal plasma metabolic data.
- In vitro methods are available to permit metabolic characterization.
- Mylan proposes to conduct characterization studies and submit NDA with 9 month data.

Drug Interactions

- In animals, there is an interaction between _____ and tolcapone that causes an increase in bioavailability of apomorphine. The interaction between _____ and other PD drugs is necessary for supporting combination drug therapy.
- Mylan will make an addendum to the current toxicology package.

IV Preclinical

Chronic Toxicity / Carcinogenicity Studies

- For a _____ indication such as PD, chronic toxicity and carcinogenicity studies are generally required. According to the sponsor, chronic toxicity studies (26-week rat, 39-week monkey) are ongoing. Final reports of these studies should be provided at the time of the NDA filing.
- Carcinogenicity studies have not been conducted, but will be required. Whether they would be necessary for marketing or could be conducted as a Phase 4 commitment would depend, to some extent, on the results of the clinical trials. If needed for marketing, completed final study reports should be included in the NDA at the time of filing.
- The _____

carcinogenic potential might be considered in light of the in vitro genotoxic effects of apomorphine (—)

Reproduction Studies

▸ Assessment of reproductive effects of a drug is generally required. However, due to the intended patient population, PD, reproduction studies may not be necessary, or may be conducted postmarketing as a Phase 4 commitment. Further discussion on this topic may be warranted.

Combination Toxicity Studies

- Ordinarily, PD drugs that will be administered in combination with other PD drugs require combination animal toxicity studies. Minimally, a combination of — and levodopa should be conducted, but combination studies with other PD drugs may be necessary depending upon intended clinical use.
- Mylan proposes to provide literature to support combination use. Combination toxicity studies are normally of 3-month duration.

PK/ADME

- The need for adequate data on the pharmacokinetics and metabolism of apomorphine (—) in the animal species used for toxicity testing was discussed.

NDA

- The sponsor committed to providing nonclinical study reports in electronic format.

V Safety Assessment

Total Patient Exposure

- Mylan believes that the total patient exposure base is sufficient to support a NDA. The exposure will consist of a considerable amount of clinical literature references (>70 publications), 813 patients from over 56 unblinded trials, 10 patients from one single blind trial, and 137 patients from nine double blind trials.
- The total patient exposure is the number of patients with adequate data followed forward in time at or above the proposed dose and with the proposed route of administration. Based upon this definition, the total patient exposure by any route is around 200, and total patient exposure by subcutaneous and intravenous administration is about 100.
- This patient exposure base is very small compared to the ordinary requirements of 1,500 total patient exposure, 300 – 600 patient exposures for 6 months, and 100 patient exposures for 1 year.
- The exact number of patient exposures considered to be adequate for safety can be negotiated. A reasonable number of patients followed forward in time should be proposed. Adequate documentation of acute adverse events that can lead to hospitalizations, e.g., orthostatic hypotension should be provided.
- Mylan should provide justification for the acceptance of the total patient

exposure base, and why this number is adequate

- Mylan may suggest the registration of the first 10,000 patients, post-approval, in order to gain long-term data
- A relatively large number of serious AEs given the very small patient database is discouraging

VI Statistical Concerns

Unblinding Study APO301

- Study APO301, that uses a prospective crossover design, will be unblinded in a week
- The Agency statistician has a concern about the possible invalidation of effects by using a prospective crossover design

Model Selection and Statistical Methods

- Also, the model has too many terms and may be inadequate for use with this small number of patients
- It is suggested that Mylan submit their statistical methods to the Agency and wait for comments before breaking the blind
- A separate statistical meeting is acceptable

VII NDA Administrative Topics

Study Reports

- Mylan proposes to submit progress reports with the initial NDA submission. Final study reports are preferred with the original NDA submission, especially if Priority review is to be granted
- Mylan was referred to industry guidance for adequate NDA components

Rolling Review

- Orphan Drugs suggested a consideration of a rolling NDA review. ▸ Under a rolling review, the review clock starts when the last piece of information is submitted. Then the due date will be 6 months from the start of the review clock

Electronic Submission

- Any amount of data submitted electronically would be helpful

VIII CMC Potency Issue

- During the separate CMC pre-NDA meeting held on December 6, 1999, there was a discussion regarding the potency of the Mylan product as compared to the U.K. marketed product, Britaject
- [—] has a — higher potency than Britaject. The potential clinical effect of this higher potency should be addressed in the NDA

ACTION ITEMS

- 1 Mylan should make the case with supporting evidence that the shortening of the "off" episodes
— Mylan should show that these patients' PD treatments had been maximized and that they would not be expected to experience additional benefit from additional PD therapy as currently recommended
- 2 Mylan proposes to conduct metabolic characterization studies and submit NDA with 9-month data
- 3 Mylan will submit an addendum to the current toxicology package to incorporate drug interaction
- 4 Mylan should provide justification for the acceptance of the total patient exposure base, and why this number is adequate
- 5 It is suggested that Mylan submit their statistical methods to the Agency and wait for comments before breaking the blind
- 6 A separate statistical meeting is acceptable
- 7 — has a — higher potency than Britaject The potential clinical effect of this higher potency should be addressed in the NDA

Signature, minutes preparer

Concurrence Chair

cc

IND52,844

HFD-120

HFD-120/Katz

/Kapcala

/Fitzgerald

/Rosloff

/Freed

/Wheelous

HFD-860/Tammara

HFD-710/Yan / Jin

Orphan Drugs / McCormick / Startzman

HFD-101/Temple

Draft January 13, 2000

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Pre-NDA MEETING MINUTES

Memorandum of Telephone Conference

Date of Teleconference June 23, 1999

Participants

Mylan

John P O'Donnell, Ph D , Executive Vice President of Research
Thomas S Clark, M D , Medical Director
Patrick McGrath, Ph D , Associate Director, Clinical Research
Frank R Sisto, Vice President, Regulatory Affairs
Andrea B Miller, R Ph , Associate Director, Regulatory Affairs
Richard Dewey, M D , Consultant - Principal Investigator - APO-202

FDA

Robert Temple, M D , Director, Office of Drug Evaluation I
Linda Carter, Associate Director Regulatory Affairs, Office of Drug Evaluation I

Purpose of Teleconference

In a letter dated April 27, 1999, Mylan requested a meeting with Dr Temple to appeal decisions made at an End-of Phase 2 Meeting held January 21, 1999 between Mylan and Division of Neuropharmacologic Drug Products Dr Temple decided to address the issues raised by Mylan in a teleconference rather than a face-to-face meeting

The issues were discussed as follows

- 1 Whether use of subcutaneous apomorphine as Parkinson's Disease is a new claim,**

Dr Temple believes that it is a new claim, but he noted that a question raised is whether patients could have been better treated by increasing the dosage level of their other medications

Mylan said that any patient can have medication increased to the point where there are no "off" periods, but only with unacceptable, immobilizing dyskinesias. The time off has to be balanced against the extent of serious dyskinesias. Dyskinesias result from Apomorphine too, but they are short-lived and there is no residual effect. Dr Temple said that the distinction between lower doses of [] and higher doses of standard agents should be addressed in the application.

2 Whether the data from one adequate and well-controlled trial and confirmatory evidence is sufficient to establish effectiveness of apomorphine for the indication, i.e., the suitability of the completed studies, given the new FDAMA Guidelines, to support the clinical safety and efficacy of subcutaneous apomorphine in the treatment of "off" episodes in PD. Mylan contended that under FDAMA, one study would meet the standard for demonstrating efficacy.

Dr Temple pointed out that FDAMA did not make reliance on one adequate and well-controlled study routine. Although in some cases the agency may agree that one study is adequate, that is usually when the effect is on mortality or major morbidity and the results very strong. Dr Temple referred the applicant to the FDA guidance entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" at <http://www.fda.gov/CDER/guidance/index.htm>

Mylan has three studies, but Mylan representatives noted that two of them were not sponsored by Mylan. Dr Temple said that there is no requirement that data must be generated by the applicant. If the studies are well-controlled and Mylan has access to the raw data they can be used. Mylan said that the studies meet FDA standards, and that they have access to the data.

Dr Temple mentioned that Mylan's letter stated that the duration of the studies required to support efficacy of apomorphine subcutaneous injection should be less than those routinely, although

not always, required for prophylactic therapy in PD (i e , 12 weeks) The studies conducted by Mylan have been of considerably shorter duration

Dr Temple said that this assumption is incorrect For a drug intended for long-term use, FDA would expect evidence that chronic use is well-tolerated and that the treatment effect persists in chronic use

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Mylan asked if they could submit the NDA before they have all the data from the study in England Dr Temple responded that they could do so, however, if the additional data is submitted within three months of the goal date, the clock date for FDA action will be extended by 3 months This led to a discussion concerning the therapeutic classification of the product Whether it is classified as standard or priority will be decided once FDA has looked at the data

4 The acceptability of the pre-clinical data to support the safety of subcutaneous apomorphine for its intended use

Dr Temple said that because the product will be approved for long-term use, Mylan will need chronic use data in animals

R Temple
L Carter 7/13/99

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cc

IND 52,844

HFD- 120/R Katz

HFD-120/T Wheelous

HFD-120/R Tresley

HFD-120/G Fitzgerald

HFD-120/L Freed

HFD-860/I Mahmood

HFD-710/K Jin

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

/s/

Teresa Wheelous
5/30/01 04 18 23 PM
CSO

>There are marketed products (e.g. Mirapex and Requip) that also show a reduction in the "off" periods in the treatment of Parkinson's Disease. These approved products have a claim that is effectively no different from that of subcutaneous apomorphine because the end result is the same: a reduction in the "off" periods.

>During an internal discussion with Division and Office level representatives it was decided that []

>Mylan states that acute use is different from long-term use because some patients experience refractory "off" periods despite optimal treatment with other PD drugs. Mylan should provide the Agency with evidence that will sufficiently justify the proposal that subcutaneous apomorphine treats an unmet need.

>Mylan believes the advantages of obtaining a fast track designation are (1) a shortened review period and (2) partnership with the Division. It was noted that the Division would work with the sponsor with or without fast track designation.

2. Mylan believes that the results of APO202 and APO101 in conjunction with supportive data are sufficient, given that Congress has recently indicated in the FDAMA of 1997 that the Agency may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence to establish effectiveness. Does the Agency agree that the studies performed to date would be adequate to establish the efficacy of subcutaneous apomorphine in short-term [] therapy?

> []

>For ethical reasons the sponsor would rather not use placebo controlled trials. It was suggested that the sponsor consider a randomized withdrawal design trial instead of placebo control. []

>The NDA requirements for this application are 2 adequate and well-controlled trials, one of which should be of at least 3-month duration. The studies should be completed prior to submission of the application. Mylan representatives believe that this application would be complete with one study and published literature articles as confirmatory evidence. The sponsor may submit its written argument to the file for Agency consideration, if it so chooses.

- 3 Subcutaneous apomorphine would be indicated for [] This represents a claim different from those of typical anti-Parkinson's therapies Does the Division agree that the studies to support such an indication could be of shorter duration than those required for chronic symptomatic treatment?**

> Ordinarily PD trials are conducted for a minimum of 3 months. The studies conducted by Mylan have been of considerably shorter duration. Conceivably, a Parkinson's patient could administer up to 5 doses daily for the remainder of their life. Studies have not been conducted that support the effectiveness in chronic use. Dr. Temple concurs that due to the potential for this product to be used daily for an extended period of time, a minimum trial duration of 3 months is necessary.

> Mylan contends that if this is a public health benefit, then the product should be approved while studies are ongoing as a Phase IV trial. However, generally Phase IV clinical trials are utilized for validation of surrogate markers.

> Mylan has observed that while PD patients have been optimized on the currently available treatment, some patients continue to exhibit "off" periods that are relieved by subcutaneous apomorphine. The documentation supporting this observation should be provided.

> Additionally, there is a concern about the occurrence of dyskinesias with optimal treatment alone, as well as with apomorphine in combination with optimal treatment. Apomorphine alone causes dyskinesias and may necessitate a reduction in the dose of the other medications. Mylan should submit direct comparative data to support the reduction in "off" period, and the Division will respond to Mylan after an internal discussion.

> The clinical safety database is inadequate, and the rationale for reduction in the database number should be provided. There should be a well-documented and sufficiently large cohort followed forward in time. The sponsor was referred to ICH guidelines for safety data reporting.

- 4 Would the completed toxicology studies (a thirteen-week rat and a thirteen-week monkey) submitted in the original IND (serial 000) be adequate to support a short-term indication (1-5 day periods of time when PD patients are unable to take their usual PD medications, i.e., NPO for diagnostic or surgical procedures)?**

> The thirteen-week subcutaneous toxicity studies in rat and monkey are not sufficient to support an NDA for [] indication such as treatment of on-off fluctuations in Parkinson's Disease. For a [] indication, 6- and 9-12 month toxicity studies in rodent and non-rodent, respectively, are usually required, as are

reproduction carcinogenicity and genotoxicity studies. Recommendations to reduce or delay (i.e. to Phase IV) these requirements may be made however, any such recommendations would need to be justified.

►The use of apomorphine injection for the proposed short-term indication was not clear therefore the preclinical data needed to support such an indication could not be addressed.

►Mylan is conducting a continuous i.v. study and intends to submit the data from this study as part of the NDA. The relevance of this study to the intended clinical dosing route/regimen should be discussed.

►Although not discussed in the meeting if apomorphine is always to be given to patients receiving Sinemet combination toxicology studies would be needed.

ACTION ITEMS

Mylan will consider the Division's comments and provide the rationale for all of the desired exceptions to the normal requirements to include:

- (1) How acute use differs — in reduction of time "off" periods
- (2) Shorter trial duration than the normal 3-month study duration requirement for both clinical and preclinical
- (3) One study with published articles qualifying as a complete NDA
- (4) Adequacy of safety database
- (5) Relevance of the i.v. trial experience compared to the subcutaneous trial experience

cc

IND 52 844

HFD-120/R Katz

HFD-120/R Tresley

HFD-120/G Fitzgerald

HFD-120/ L Freed

HFD-120/T Wheelous

HFD-860/I Mahmood

HFD0710/K Jin

Draft Jan 28 1999

Final April 13 1999.

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End-Of-Phase 2 MEETING MINUTES

FROM.

Teresa Wheelous

SUBJECT.

Fast Track Designation Granted
IND 52,844, — (Apomorphine) Injection

Based upon a June 23, 1999 Telecon between Mylan Pharmaceutical representatives and Dr Robert Temple, Office of Drug Evaluation I Director, an understanding was reached that this application would be granted fast track designation

The attached are the Agency minutes of the June 23, 1999 telephone conversation in which the fast track understanding is reached

**APPEARS THIS WAY
ON ORIGINAL**