

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-264

Administrative/Correspondence

NDA Section 13 Patent Information

The Section 13 Patent Information for — (apomorphine hydrochloride, USP) Injection New Drug Application is found on the following page

**APPEARS THIS WAY
ON ORIGINAL**

Item 13 Patent Information

The undersigned declares that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the product

By Shy MD

Name Shelly Monteleone

Title Assistant Patent Counsel

NDA Section 14 Patent Certification

The application does not contain Patent Certification information

**APPEARS THIS WAY
ON ORIGINAL**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # 21-264 Supplement Type (e.g. SE5) _____ Supplement Number _____

Stamp Date January 2, 2003, Resubmitted October 17, 2003 Action Date April 20, 2004

HFD 120 Trade and generic names/dosage form Apokyn (apomorphine hydrochloride) Injection

Applicant Bertek Pharmaceuticals Therapeutic Class NME

Indication(s) previously approved

Each approved indication must have pediatric studies Completed, Deferred, and/or Waived

Number of indications for this application(s) 1

Indication #1 the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease

Is there a full waiver for this indication (check one)?

- Yes Please proceed to Section A
- No Please check all that apply Partial Waiver Deferred Completed
NOTE More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary

Section A Fully Waived Studies

Reason(s) for full waiver

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
Too few children with disease to study
- There are safety concerns
- Other _____

If studies are fully waived then pediatric information is complete for this indication. If there is another indication please see Attachment A. Otherwise this Pediatric Page is complete and should be entered into DFS.

Section B Partially Waived Studies

Age/weight range being partially waived

Min _____ kg _____ mo _____ yr _____ Tanner Stage _____
Max _____ kg _____ mo _____ yr _____ Tanner Stage _____

Reason(s) for partial waiver

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other _____

If studies are deferred proceed to Section C If studies are completed proceed to Section D Otherwise this Pediatric Page is complete and should be entered into DFS

Section C Deferred Studies

Age/weight range being deferred

Min _____ kg _____ mo _____ yr _____ Tanner Stage _____
Max _____ kg _____ mo _____ yr _____ Tanner Stage _____

Reason(s) for deferral

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other _____

Date studies are due (mm/dd/yy) _____

If studies are completed proceed to Section D Otherwise this Pediatric Page is complete and should be entered into DFS

Section D Completed Studies

Age/weight range of completed studies

Min _____ kg _____ mo _____ yr _____ Tanner Stage _____
Max _____ kg _____ mo _____ yr _____ Tanner Stage _____

Comments

If there are additional indications please proceed to Attachment A Otherwise this Pediatric Page is complete and should be entered into DFS

This page was completed by

{See appended electronic signature page}

Regulatory Project Manager

cc NDA 21-264
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337

(revised 12-22-03)

The Section 16 Debarment Certification for — (apomorphine hydrochloride, USP) Injection
New Drug Application is found on the following page

**APPEARS THIS WAY
ON ORIGINAL**



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P O Box 4310 • Morgantown West Virginia 26504-4310 U S A • (304) 599-2595

April 17, 2000

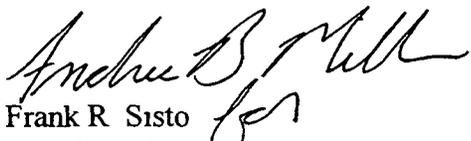
Russell G Katz, M D , Director
Division of Neuropharmacologic Drug Products, HFD 120
Central Document Room (Room #4-2833)
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE ——— INJECTION, 10 mg/mL
(apomorphine hydrochloride, USP)
NDA #21-264

Dear Dr Katz

Pursuant to 21 CFR 314 50(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U S C 335a(k)), as amended by the Generic Drug Enforcement Act of 1992, Mylan hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Act in connection with the application for the referenced product

Sincerely,


Frank R Sisto
Vice President
Regulatory Affairs

FRS/dn

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599 7284
Business Development (304) 599 7284
Human Resources (304) 598 5406

Information Systems
Label Control (800) 848-0463
Legal Services (304) 598 5408
Maintenance & Engineering (304) 598 5411
Medical Unit (304) 598 5445

(304) 285-6404
(800) 848-0463
(304) 598 5408
(304) 598 5411
(304) 598 5445

Purchasing (304) 598 5401
Quality Control (304) 598 5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

VOLUME 1

| Application Information | | |
|---|---|---|
| NDA 21-264 | | |
| Drug: APOKYN (Apomorphine Hydrochloride Injection 10 mg/ml) | | Applicant Bertek Pharmaceuticals, Inc |
| RPM CDR Teresa Wheelous | HFD- 120 | Phone # 594-5504 |
| Application Type <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | Reference Listed Drug (NDA #, Drug name) | |
| ❖ Application Classifications | | |
| • Review priority | <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority | |
| • Chem class (NDAs only) Type 1 | | |
| • Other (e g , orphan, OTC) Orphan | | |
| ❖ User Fee Goal Dates | | April 20, 2004 |
| ❖ Special programs (indicate all that apply) | | <input type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314 510 (accelerated approval) <input type="checkbox"/> 21 CFR 314 520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review |
| A User Fee Information | | |
| • User Fee | <input type="checkbox"/> Paid | |
| • User Fee waiver | <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other | |
| • User Fee exception | <input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other | |
| ❖ Application Integrity Policy (AIP) | | |
| • Applicant is on the AIP | <input type="checkbox"/> Yes <input type="checkbox"/> No | |
| • This application is on the AIP | <input type="checkbox"/> Yes <input type="checkbox"/> No | |
| • Exception for review (Center Director's memo) | | |
| • OC clearance for approval | | |
| B | | <input type="checkbox"/> Verified |
| ❖ Debarment certification verified that qualifying language (e g , willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U S agent | | |
| C | | |
| ❖ Patent | | |
| • Information Verify that patent information was submitted | <input checked="" type="checkbox"/> Verified | |
| • Patent certification [505(b)(2) applications] Verify type of certifications submitted | 21 CFR 314 50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314 50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) | |
| • For paragraph IV certification verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice) | <input type="checkbox"/> Verified | |

| | |
|---|--|
| D Exclusivity Summary (approvals only) | |
| E Administrative Reviews (Project Manager, ADRA) (indicate date of each review) | |
| General Information | |
| F Actions | |
| <ul style="list-style-type: none"> Proposed action | (x) AP () TA () AE () NA |
| <ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) | 6/16/00 RTF Action Letter 7/2/03 Approvable Letter |
| <ul style="list-style-type: none"> Status of advertising (approvals only) | (x) Materials requested in AP letter () Reviewed for Subpart H |
| G Public communications | |
| <ul style="list-style-type: none"> Press Office notified of action (approval only) | () Yes () Not applicable |
| <ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated | () None () Press Release () Talk Paper () Dear Health Care Professional Letter |
| H Labeling (package insert, patient package insert (if applicable), Med Guide (if applicable)) | |
| <ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) | |
| <ul style="list-style-type: none"> Most recent applicant-proposed labeling | |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | |
| <ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings) | DDMAC 3/2/04DSRCS 2/18/04, DDMAC 7/21/03, ODS 6/23/03, CDRH 5/21/03, DMETS 4/22/03, DMETS 8/15/02 OPDRA 7/24/00 |
| <ul style="list-style-type: none"> Other relevant labeling (e g , most recent 3 in class, class labeling) | Dopamine Agonists -REQUIP, MIRAPEX |
| I Labels (immediate container & carton labels) | |
| <ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) | July 2, 2003 |
| <ul style="list-style-type: none"> Applicant proposed | |
| <ul style="list-style-type: none"> Reviews | |
| J Post-marketing commitments | |
| <ul style="list-style-type: none"> Agency request for post-marketing commitments | |
| <ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments | |
| K Outgoing correspondence (i e , letters, E-mails, faxes) | |
| L Memoranda and Telecons | |
| M Minutes of Meetings | |
| <ul style="list-style-type: none"> EOP2 meeting (indicate date) | 1/21/99 |
| <ul style="list-style-type: none"> Pre-NDA meeting (indicate date) | 12/10/99, 1/10/02, 1/16/02 (CMC) |
| <ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date, approvals only) | |
| <ul style="list-style-type: none"> Other | Internal 1/31/03, 6//25/00 Informal Meeting after RTF, 6/16/00 RTF Letter, Fast Track Dispute 6/23/99 |
| <ul style="list-style-type: none"> Advisory Committee Meeting | |
| <ul style="list-style-type: none"> Date of Meeting | |
| <ul style="list-style-type: none"> 48-hour alert | |
| <ul style="list-style-type: none"> Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | |

| | |
|--|--|
| VOLUME 2 | |
| | |
| <input type="checkbox"/> Summary Reviews (e g , Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i> | |
| <input type="checkbox"/> Clinical review(s) <i>(indicate date for each review)</i> | |

APPEARS THIS WAY
ON ORIGINAL

VOLUME 3

| | |
|--|---|
| D Microbiology (efficacy) review(s) (indicate date for each review) | 5/14/03, 4/9/03, 6/12/00 |
| Q Safety Update review(s) (indicate date or location if incorporated in another review) | |
| V Pediatric Page(separate page for each indication addressing status of all age groups) | |
| R Statistical review(s) (indicate date for each review) | 3/22/04, 6/6/03 |
| S Biopharmaceutical review(s) (indicate date for each review) | 3/10/04, 8/11/03, 6/24/03,7/20/00 |
| T Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review) | 8/26/03 |
| U Clinical Inspection Review Summary (DSI) | |
| <ul style="list-style-type: none"> • Clinical studies • Bioequivalence studies | July 1, 2003 (DSI), 6/19/03 |
| V CMC Information | |
| CMC review(s) (indicate date for each review) | 3/9/04, 6/13/03 |
| V Environmental Assessment | |
| <ul style="list-style-type: none"> • Categorical Exclusion (Review dated 6/13/03) • Review & FONSI (indicate date of review) • Review & Environmental Impact Statement (indicate date of each review) | |
| V Micro (validation of sterilization & product sterility) review(s) (indicate date for each review) | |
| V Facilities inspection (provide EER report) | Date completed 9/25/03 (x) Acceptable () Withhold recommendation |
| V Methods validation | () Completed (x) Requested () Not yet requested |
| W Nonclinical Pharm/Tox Information | |
| V Pharm/tox review(s), including referenced IND reviews (indicate date for each review) | 3/31/04, 6/18/03, 6/17/03 |
| V Nonclinical inspection review summary | |
| V Statistical review(s) of carcinogenicity studies (indicate date for each review) | |
| V CAC/ECAC report | |
| X DEVICES Review | 5/28/03 |

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

VOLUME 1

| Application Information | | |
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| NDA 21-264 | | |
| Drug: APOKYN (Apomorphine Hydrochloride Injection 10 mg/ml) | | Applicant Bertek Pharmaceuticals, Inc |
| RPM CDR Teresa Wheelous | HFD- 120 | Phone # 594-5504 |
| Application Type (X) 505(b)(1) () 505(b)(2) | Reference Listed Drug (NDA #, Drug name) | |
| ❖ Application Classifications | | |
| <ul style="list-style-type: none"> • Review priority | () Standard (X) Priority | |
| <ul style="list-style-type: none"> • Chem class (NDAs only) Type 1 | | |
| <ul style="list-style-type: none"> • Other (e g , orphan, OTC) Orphan | | |
| ❖ User Fee Goal Dates | | April 20, 2004 |
| ❖ Special programs (indicate all that apply) | | () None Subpart H () 21 CFR 314 510 (accelerated approval) () 21 CFR 314 520 (restricted distribution) (x) Fast Track (x) Rolling Review |
| \\ User Fee Information | | |
| <ul style="list-style-type: none"> • User Fee | () Paid | |
| <ul style="list-style-type: none"> • User Fee waiver | () Small business () Public health () Barrier-to-Innovation () Other | |
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| <ul style="list-style-type: none"> • Applicant is on the AIP | () Yes () No | |
| <ul style="list-style-type: none"> • This application is on the AIP | () Yes () No | |
| <ul style="list-style-type: none"> • Exception for review (Center Director's memo) | | |
| <ul style="list-style-type: none"> • OC clearance for approval |) 3/31/04 | |
| B | | () Verified |
| ❖ Debarment certification verified that qualifying language (e g , willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U S agent | | |
| C | | |
| ❖ Patent | | |
| <ul style="list-style-type: none"> • Information Verify that patent information was submitted | (X) Verified | |
| <ul style="list-style-type: none"> • Patent certification [505(b)(2) applications] Verify type of certifications submitted | 21 CFR 314 50(i)(1)(i)(A) () I () II () III () IV | |
| | 21 CFR 314 50(i)(1) - - - - () (ii) () (iii) | |
| <ul style="list-style-type: none"> • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice) | () Verified | |

| | |
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| <ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) | |
| <ul style="list-style-type: none"> Most recent applicant-proposed labeling | |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | |
| <ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings) | DDMAC 3/2/04, DSRCs 2/18/04, DMETS 12/16/03, DDMAC 7/21/03, ODS 6/23/03, CDRH 5/21/03, DMETS 4/22/03, DMETS 8/15/02 OPDRA 7/24/00 |
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| I Labels (immediate container & carton labels) | |
| <ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) | July 2, 2003 |
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| <ul style="list-style-type: none"> Reviews | |
| J Post-marketing commitments | |
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| ❖ Advisory Committee Meeting | |
| <ul style="list-style-type: none"> Date of Meeting | |
| <ul style="list-style-type: none"> 48-hour alert | |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | |

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|---|--|
| VOLUME 2 | |
| | |
| <input checked="" type="checkbox"/> Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i> | |
| <input type="checkbox"/> Clinical review(s) <i>(indicate date for each review)</i> | |

APPEARS THIS WAY
ON ORIGINAL

VOLUME 3

| | |
|--|---|
| P Microbiology (efficacy) review(s) (<i>indicate date for each review</i>) | 5/14/03, 4/9/03, 6/12/00 |
| Q Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>) | |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | |
| R Statistical review(s) (<i>indicate date for each review</i>) | 3/22/04, 6/616/03 |
| S Biopharmaceutical review(s) (<i>indicate date for each review</i>) | 3/10/04, 8/11/03, 6/24/03,7/20/00 |
| T Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>) | 8/26/03 |
| U Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | July 1, 2003 (DSI), 6/19/03 |
| • Bioequivalence studies | |
| V CMC Information | |
| CMC review(s) (<i>indicate date for each review</i>) | 3/9/04, 6/13/03 |
| ❖ Environmental Assessment | |
| • Categorical Exclusion (Review dated 6/13/03) | |
| • Review & FONSI (<i>indicate date of review</i>) | |
| • Review & Environmental Impact Statement (<i>indicate date of each review</i>) | |
| ❖ Micro (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>) | |
| ❖ Facilities inspection (provide EER report) | Date completed 9/25/03 (x) Acceptable () Withhold recommendation |
| ❖ Methods validation | () Completed (x) Requested () Not yet requested |
| W Nonclinical Pharm/Tox Information | |
| ❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | 6/18/03, 6/17/03 |
| ❖ Nonclinical inspection review summary | |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | |
| ❖ CAC/ECAC report | |
| X DEVICES Review | 5/28/03 |

Redacted 2

pages of trade

secret and/or

confidential

commercial

information



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I**

FACSIMILE TRANSMITTAL SHEET

DATE: March 8, 2004

| | |
|--|--|
| To: Andrea Miller | Teresa Wheelous |
| Company: Bertek Pharmaceuticals Inc. | From Division of Division of Neuropharmacological Drug Products |
| Fax number (304) 285-6407 | Fax number (301) 594-2859 |
| Phone number (304) 599-25-95x6869 | Phone number (301) 594-2850 |
| Subject ODS Comments for NDA 21-264 PPI | |

Total no of pages including cover 16

Andrea,

The following are ODS Labeling comments regarding the PPI for Apokyn

SUBJECT ODS/DSRCS Review of Patient Labeling for Apokyn
(apomorphine hydrochloride, USP), NDA 21-264

The patient labeling which follows represents the revised risk communication materials of the patient information and Instructions for Use for Apokyn (apomorphine hydrochloride, USP), NDA 21-264 The Division of Surveillance, Research, and Communication Support (DSRCS) reviewed the patient information from a patient comprehension perspective The Division of Medication Errors and Technical Support (DMETS) reviewed the instructions for the patient information in an attempt to focus on safety issues to prevent possible medication errors We have simplified the wording in the PPI and Instructions for Use, made the PPI consistent with the PI, removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put the PPI in the format that we are recommending for all patient information Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds

These revisions are based on labeling (PI) submitted by the sponsor on October 17, 2003 Patient information should always be consistent with the prescribing information All future changes to the PI should also be reflected in the PPI

Document to be mailed YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized If you have received this document in

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

MEMORANDUM

To Teresa Wheelous, RPh
Division of Neuropharmacological Drug Products, HFD-120

From Iris Masucci, PharmD
DDMAC, HFD-042

CC Jeanine Best, MSN, RN, PNP
Division of Surveillance, Research, and Communication Support,
HFD-410

Date March 2, 2004

Re Comments on Apokyn (apomorphine) draft patient labeling
NDA 21-264

DDMAC has reviewed the proposed patient labeling for Apokyn based on the following documents

- "Patient Package Insert" (dated 10/17/03) that accompanied the Dec 03 consult request from HFD-120 to DDMAC
- ODS/DSRCS comments from Jeanine Best to HFD-120 dated 2/18/04
- the sponsor's revised draft prescribing information dated Dec 03 that followed the July 03 approvable letter

DDMAC concurs with ODS in its revisions of the information into the more standardized format used for patient labeling, and we thus used their revision as the basis for our review. We add the following additional comments

• / []

•

[]

• {

}

• [

]

• [

]

• [

]

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/

Iris Masucci
3/2/04 04 08 41 PM
DDMAC REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE February 18, 2004

TO Russell Katz, M D , Director
Division of Neuropharmacological Drug Products
HFD-120

VIA Teresa Wheelous, R Ph , Senior Regulatory Management Officer
Division of Neuropharmacological Drug Products
HFD-120

FROM Jeanne Best, M S N , R N , P N P
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH Gerald Dal Pan, M D , M H S , Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT ODS/DSRCS Review of Patient Labeling for Apokyn
(apomorphine hydrochloride, USP), NDA 21-264

The patient labeling which follows represents the revised risk communication materials of the patient information and Instructions for Use for Apokyn (apomorphine hydrochloride, USP), NDA 21-264. The Division of Surveillance, Research, and Communication Support (DSRCS) reviewed the patient information from a patient comprehension perspective. The Division of Medication Errors and Technical Support (DMETS) reviewed the instructions for the patient information in an attempt to focus on safety issues to prevent possible medication errors. We have simplified the wording in the PPI and Instructions for Use, made the PPI consistent with the PI, removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put the PPI in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on labeling (PI) submitted by the sponsor on October 17, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division. Please call us if you have any questions.

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

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

/s/

Jeanine Best
2/18/04 11 27 56 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/19/04 04 19 36 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

Wheelous, Teresa A

From Wheelous, Teresa A
Sent Monday, December 22, 2003 10:35 AM
To 'Andrea Miller@mylanlabs.com'
Subject Apomorphine Reanalysis Request

Andrea,

The medical reviewer has the following request

Please reanalyze your spontaneous "off" (for 1 hour rule and 75 % rule separately) and induced "off" data (attachment 313) to show results of studies APO 301 and APO302 separately (without pooling as you have done). In these reanalyses of each study separately, please also reanalyze data among groups of patients by pooling responses of patients without regard to the average time of sleep. For example, results of patients with an average of 6, 6.5, or 7 hours would be pooled.

Thank you,

CDR Teresa Wheelous, R. Ph
Senior Regulatory Management Officer
Division of Neuropharmacological Drug Products
(301) 594-2850

Wheelous, Teresa A

From Wheelous, Teresa A
Sent Monday, December 22, 2003 10:44 AM
To 'Andrea Miller@mylanlabs.com'
Subject Apomorphine Labeling Request

Andrea,

Please send me Word version of the annotated and unannotated labeling for Apomorphine. Please compare the labeling that we provided in the Approvable letter to your recently proposed labeling.

Thanks,
Teresa
CDR Teresa Wheelous, R. Ph
Senior Regulatory Management Officer
Division of Neuropharmacological Drug Products
(301) 594-2850



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I**

FACSIMILE TRANSMITTAL SHEET

DATE: December 16, 2003

| | |
|--|---|
| To: Andrea Miller | From Teresa Wheelous |
| Company. Bertek Pharmaceuticals Inc. | Division of Division of Neuropharmacological Drug Products |
| Fax number (304) 285-6407 | Fax number (301) 594-2859 |
| Phone number (800) 826-9526 x6869 | Phone number (301) 594-2850 |
| Subject NDA 21-264 Apomorphine HCl Injection DMETS Comments | |

Total no of pages including cover 3

Andrea,

The following are DMETS comments regarding the proposed name Apokyn

- 1 DMETS has no objections to the use of the proposed proprietary name, Apokyn
This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document
- 2 In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product
- 3 DDMAC finds the name Apokyn acceptable from a promotional perspective

Document to be mailed

YES

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 594-2850. Thank you

III LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Apokyn, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A GENERAL COMMENTS

1 The terminology "units", "cc", and "mL" are used interchangeably throughout the container labels, carton and insert labeling. To minimize potential confusion, a single term should be used consistently throughout the literature.

2 DMETS is concerned with the proposed cartridge packaging configuration. The container label and carton labeling does not clearly state that the Apokyn cartridge must ONLY be used with the Apokyn Pen Pak. The Apokyn cartridge resembles other currently marketed cartridges which can be administered intravenously. Apokyn can only be administered subcutaneously due to the serious adverse events (such as intravenous crystallization of apomorphine, leading to thrombus formations and pulmonary embolism) following intravenous use of apomorphine. DMETS is concerned about a potential drug misadventure, should the user attach the cartridge to another device (e.g. tubex injector) and inject the Apokyn cartridge intravenously. Please assure that a needle cannot be attached or that this cartridge can not be delivered via a needleless system. We recommend including a statement on the cartridge container label and carton labeling which clearly states that the Apokyn cartridge must ONLY be used with the Apokyn Pen Pak. In addition, we recommend including a statement which indicates that the device must only be used subcutaneously.

3 The carton label for the Apokyn Pen Pak indicates in prominent letters that it is "For use with Apokyn 3 mL Cartridges (see below)". Users could potentially be misled to believe that the cartridges will be included in the Pen Pak contents. DMETS recommends

Additionally, we recommend

deleting

B CONTAINER LABEL (Ampule and Cartridge)

4 See GENERAL COMMENTS

5 We recommend that the established name be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10(g)(2).

6 Increase the prominence of the product strength.

7 We were unable to compare the two different label designs (ampule vs. cartridge) with the black and white copies that were provided. Please ensure the labels and labeling are clearly differentiated using contrasting colors, boxing, or some other means.

8 DMETS recommends

9 The "AMPULE" and "CARTRIDGE" statements appear in capital letters on the principal display panel adjacent to or immediately below the proprietary name. DMETS recommends that this statement be deleted or placed with less prominence so that it does not interfere with the readability of the proprietary name. For example **APOKYN™ Ampule**. If the descriptors "ampule" and "cartridge" are deleted, we recommend revising "2 mL" to "2 mL ampule" and "3 mL" to "3 mL cartridge".

10 Include the dosage form with the established name For example

APOKYN™

(Apomorphine Hydrochloride Injection)

20 mg/2 mL (10 mg/mL)

B CARTON LABELING

See GENERAL COMMENTS and B3, B4, B6, and B7 comments

C INSERT LABELING and INSTRUCTIONS FOR USE LABELING

1 See A1 comment

2 Eliminate terminal zeros in the expressions of strength throughout labels and labeling

(e g 1 cc instead of 1 0 cc)

3 INDICATIONS AND USAGE

a DMETS notes †

**APPEARS THIS WAY
ON ORIGINAL**

Wheelous, Teresa A

From Kapcala, Leonard P
Sent Friday, September 05, 2003 12:24 PM
To Wheelous, Teresa A
Cc Kapcala, Leonard P
Subject Reanalysis of AEs possibly suggestive of a Fall during Apomorphine treatment (Bertek, NDA 21264)

Hi Teresa,

After I looked at our request to the sponsor I was not sure if they would necessarily provide a tabulary summary of the analyses. I am providing 2 tables for the sponsor to complete regarding their "old" and "new" analyses. Would you please send this to the sponsor and ask them to summarize the "old" and "new" analyses in these tables?

Thanx

Len

4-5521



APMTabulationofFal
levents903 d

Wheelous, Teresa A

From Wheelous, Teresa A
Sent Friday, September 05, 2003 2:34 PM
To 'Andrea Miller (Andrea.Miller@mylanlabs.com)'
Subject Apomorphine Reanalysis Table Format

Andrea,

Dr. Kapcala isn't sure that you would provide a tabular summary of the analyses. Therefore, the following are 2 tables that should be used to complete and summarize your "old" and "new" analyses.

Table 1: Numbers of Adverse Events Possibly Suggestive of a Fall During Apomorphine Treatment

(Sponsor's Original Analysis)

| | Serious or Non-serious Events | Serious Events | Non-serious Events |
|---------------------------------|-------------------------------|----------------|--------------------|
| Total Number of Events | | | |
| Total Number of Unique Patients | | | |

Table 2: Numbers of Adverse Events Possibly Suggestive of a Fall During Apomorphine Treatment

(Sponsor's New Re-Analysis)

| | Serious or Non-serious Events | Serious Events | Non-serious Events |
|---------------------------------|-------------------------------|----------------|--------------------|
| Total Number of Events | | | |
| Total Number of Unique Patients | | | |

CDR Teresa Wheelous, R. Ph
Senior Regulatory Management Officer
Division of Neuropharmacological Drug Products
(301) 594-2850

Wheelous, Teresa A

From: Kapcala, Leonard P
Sent: Wednesday, September 03, 2003 1:26 PM
To: Wheelous, Teresa A
Cc: Kapcala, Leonard P
Subject: FW: NDA 21264 SQ APM for PD ? Ask Bertek to analyze their AEs for events possibly suggestive of falls

Hi Teresa,,

Would you please communicate the following attached request to the sponsor and please let me know when they received it? As you can see in the e-mails below, John agrees

Please ask the sponsor to contact us if there are any questions related to this request

Thanx

Len



APMFallReanalysis
doc (54 KB)

-----Original Message-----

From: Feeney III, John J
Sent: Wednesday, September 03, 2003 1:18 PM
To: Kapcala, Leonard P
Subject: RE: NDA 21264 SQ APM for PD ? Ask Bertek to analyze their AEs for events possibly suggestive of falls

I agree with your concern. Will you go ahead and send your request to the sponsor. Thanks

-----Original Message-----

From: Kapcala, Leonard P
Sent: Friday, August 29, 2003 12:26 PM
To: Feeney III, John J
Cc: Kapcala, Leonard P
Subject: NDA 21264 SQ APM for PD ? Ask Bertek to analyze their AEs for events possibly suggestive of falls

Hi John,

If you recall, Bertek submitted information just prior to our our approvable clarifying info about their mapping strategy for classifying AEs. I had detected some instances where it looked like they may not have captured all events that should reasonably be considered as possible suggestive of a falls. You did not want to get involved with this in the labeling or approvable letter at that late date. We never dealt with this further.

We noted in the labeling section on falls that ~, of patients in clinical trials had events reasonably suggestive of falls and about ~ of patients had such events that were considered serious.

It's difficult to know how much the figures might increase with this reanalysis, but they would likely increase. If you agree that we should ask the sponsor to reanalyze these data, I've attached some language for the sponsor on this issue.

Please let me know your thoughts.

Thanx

10/9/03

CONSULTATION RESPONSE**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS, HFD-420)****DATE RECEIVED** 08/20/03**DUE DATE** 10/22/03**ODS CONSULT #** 00-0137-3**TO** Russell G Katz, M D
Director, Division of Neuropharmacological Drug Products
HFD-120**THROUGH** Teresa A Wheelous
Project Manager
HFD-120**PRODUCT NAME**
Apokyn
(Apomorphine Hydrochloride Injection)
10 mg/mL
(2 mL ampules and 3 mL cartridges)**NDA SPONSOR** Bertek Pharmaceuticals Inc**NDA #** 21-264**SAFETY EVALUATOR** Jinhee L Jahng, Pharm D**SUMMARY** In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Apokyn" to determine the potential for confusion with approved proprietary and established names as well as pending names**RECOMMENDATIONS**

- 1 DMETS has no objections to the use of the proposed proprietary name, Apokyn This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document
- 2 In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product
- 3 DDMAC finds the name Apokyn acceptable from a promotional perspective

/S/

/S/

Carol Holquist, R Ph
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone (301) 827-3242 Fax (301) 443-9664Jerry Phillips, R Ph
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420, PKLN Rm 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW October 9, 2003
NDA # 21-264
NAME OF DRUG Apokyn (Apomorphine Hydrochloride Injection)
 10 mg/mL
NDA HOLDER Bertek Pharmaceuticals Inc

*****NOTE** This review contains proprietary and confidential information that should not be released to the public ***

I INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for assessment of the proprietary name "Apokyn", regarding potential name confusion with other proprietary or established drug names. The container label, carton and insert labeling were not submitted and therefore have not been reviewed at this time. The sponsor has submitted additional information, including an independent analysis conducted by _____ to DMETS for review and comment.

Apokyn is the *fourth* proposed proprietary name for this product. DMETS previously reviewed the names, _____, and found these proposed proprietary names unacceptable. Consequently, the sponsor is now submitting Apokyn as proposed proprietary name choice for apomorphine hydrochloride.

PRODUCT INFORMATION

Apokyn (Apomorphine Hydrochloride, USP) is a potent, centrally active, dopamine receptor agonist with affinity for both the D₁ and D₂ subfamilies of dopamine receptors within the corpus striatum. Apomorphine is a lipophilic compound that is rapidly absorbed and eliminated. Following subcutaneous administration it appears to have bioavailability equal to that of intravenous administration. Apokyn is indicated for _____

_____ in patients with _____ Parkinson's disease. Apokyn injection is for subcutaneous administration only. The recommended starting dose is 2 mg. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principle side effects. The daily dose should not exceed 50 mg and each individual dose should not exceed 10 mg. Apokyn will be available as a clear, colorless, sterile solution in 2 mL ampules and 3 mL cartridges.

II RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Apokyn" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U S Patent and Trademark Office's trademark electronic search system (TESS) was conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Apokyn. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

- 1 The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Apokyn. Similarly, through independent review, three additional names (Aphrodyne, Apogen, and Aprodine) were also thought to have the potential for confusion with the name Apokyn. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.
- 2 Additionally, the Panel had concerns regarding the potential for confusion with currently existing "Apo-" products manufactured by the Canadian company, Apotex. However, concerns were minimized as these products are available in Canada only.
- 3 DDMAC did not have concerns with Apokyn in regard to promotional claims.

¹MICROMEDEX Integrated Index 2003, MICROMEDEX Inc , 6200 South Syracuse Way Suite 300, Englewood Colorado 80111-4740, which includes all products/database within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems

²Facts and Comparisons 2003, Facts and Comparisons St Louis, MO

³The Drug Product Reference File [DPR] the DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book

⁴WWW location <http://www.uspto.gov/main/trademarks.htm>

⁵Data provided by Thomson & Thomson's SAEGIS (tm) Online Service available at www.thomson-thomson.com

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

| Product Name | Dosage form(s), Established name | Usual adult dose* | Other** |
|--|--|--|---------|
| Apokyn | Apomorphine Hydrochloride, USP Injection 10 mg/mL (2 mL ampules and 3 mL cartridges) | Starting dose is 2 mg SC. The daily dose should not exceed 50 mg and each individual dose should not exceed 10 mg. | |
| Epogen | Epoetin Alfa for Injection 2000 Units/mL, 3000 Units/mL, 4000 Units/mL 10000 Units/mL, 20000 Units/mL 40000 Units/mL | Starting dose is 50 to 100 Units/kg three times weekly IV or SC Maintenance dose is individually titrated | SA |
| Amikin | Amikacin Sulfate Injection 50 mg base/mL 250 mg base/mL | 15 mg/kg/day at intervals of 8 to 12 hours by intramuscular or intravenous injections | SA |
| Aphrodyne | Yohimbine Hydrochloride Tablets 5 4 mg | 1 tablet three times daily | SA |
| Aprodine (OTC) | Pseudoephedrine Hydrochloride/ Triprolidine Hydrochloride Tablets 60 mg/2 5 mg | 1 tablet every 4 to 6 hours up to 4 tablets per day | SA |
| Apogen (not marketed) | Gentamicin Sulfate Injection 10 mg base/mL 40 mg base/mL | 3 mg/kg/day IM or IV in 3 equally divided doses (maximum 5 mg/kg/day) | SA/LA |
| Capoten | Captopril Tablet 12 5 mg 25 mg, 50 mg 100 mg | 25 mg three times daily (maximum dose = 450 mg/day) | SA/LA |
| *Frequently used not all-inclusive **LA (look-alike) SA (sound-alike) ***Pending approval proprietary and confidential information that should not be released to the public | | | |

B PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

DMETS' Phonetic and Orthographic Analysis (POCA) database was unavailable to search at the time of this review

C PRESCRIPTION ANALYSIS STUDIES

1 Methodology

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Apokyn with other U S drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Apokyn (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

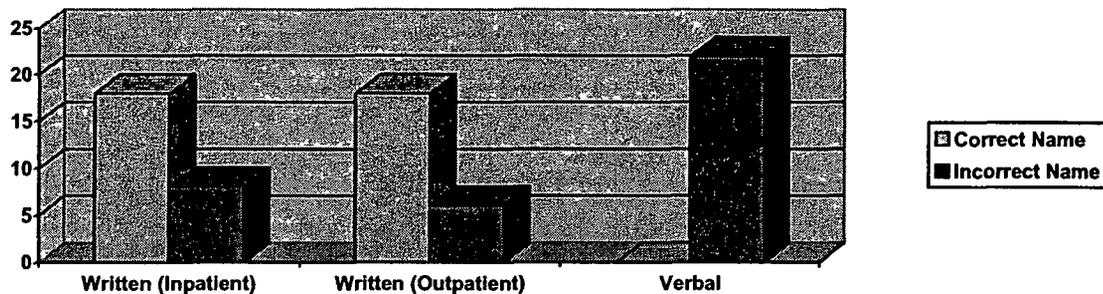
| HANDWRITTEN PRESCRIPTION | VERBAL PRESCRIPTION |
|---|---|
| <p>Outpatient RX</p> <p><i>Apokyn</i> <i>10 mg SC daily</i> <i># 10</i></p> | <p>Apokyn 10 mg SC daily # 10</p> |
| <p>Inpatient RX</p> <p><i>Apokyn 10mg SC daily</i></p> | |

2 Results

The results are summarized in Table I

Table I

| Study | # of Participants | # of Responses (%) | Correctly Interpreted | Incorrectly Interpreted |
|--------------------|-------------------|--------------------|-----------------------|-------------------------|
| Written Inpatient | 41 | 26 (63%) | 18 (69%) | 8 (31%) |
| Written Outpatient | 43 | 24 (56%) | 18 (75%) | 6 (25%) |
| Verbal | 43 | 22 (51%) | 0 (0%) | 22 (100%) |
| Total | 127 | 72 (57%) | 36 (50%) | 36 (50%) |



Among the written inpatient prescriptions, 8 of 26 (31%) participants interpreted the name correctly. Some of the incorrect interpretations from the prescription included Aspokyn, Apokyne, Apokifn, Apokin, Apopyn, Apokifer, Aporfin, and Apopifn. None of the interpretations are similar to a currently marketed drug product.

In the written outpatient prescriptions, 6 of 24 (25%) participants interpreted the name incorrectly. The incorrect interpretations from the prescription included Apo/cyn, Apokyz, Apokyr, Apokryn, Apolyn, and Apokgran. None of the interpretations are similar to a currently marketed drug product.

Among the verbal prescription study participants for Apokyn, all the participants interpreted the name incorrectly. Many of the incorrect name interpretations were misspelled/phonetic variations of "Apokyn". Some of the incorrect interpretations included Apochyme, Apokine (15), Aprokine, Effokine, Afokind, Aopkine, and Apocaine. None of the interpretations are similar to a currently marketed drug product.

D SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Apokyn, the primary concerns related to look-alike and sound-alike names already in the U.S. marketplace. The products considered to have potential for name confusion with Apokyn are Epogen, Amikin, Aphrodyne, Aprodine, Apogen, and Capoten.

Although the product, Apogen, was identified as having potential for confusion with Apokyn, no evidence was found that this product is still being marketed, and therefore will not be further reviewed.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Apokyn could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

1. Epogen and Apokyn have the potential for sound-alike confusion. Epogen is a glycoprotein which stimulates red blood cell production. Epogen is used for the treatment of anemia of chronic renal failure patients, Zidovudine-treated HIV-infected patients, and cancer patients on chemotherapy. It is also used for reduction of allogeneic blood transfusion in surgery patients. Epogen and Apokyn contain three syllables and share the same middle syllable "-po-". The first syllable "Ep-" may sound like "Ap-" if both letters are pronounced as EHP. Likewise, the "-gen" in Epogen may sound like "-kyn" in Apokyn, if "-gen" is pronounced as a hard "g" rather than a soft "g" and "-kyn" is pronounced as GHIN. Despite this similarity, differences including varying storage conditions (Epogen is refrigerated whereas Apokyn is kept at room temperature), dosage strengths, and dosage schedule, help to distinguish these products. Due to the aforementioned reasons, DMETS believes the risk for a misadventure involving Epogen and Apokyn is reduced.

2 [

1

- 3 Amikin and Apokyn were found to have sound-alike similarities. Amikin is a semi-synthetic aminoglycoside for use in treating infections caused by gram-negative organisms. Amikin and Apokyn may sound similar since each name begins with the letter "A-", ends with similar suffixes ("-kin" vs "-kyn"), and contains three syllables. When pronounced, the "-mi-" in Amikin and the "-po-" in Apokyn differentiate the two names from one another as the sounds are distinct. Amikin and Apokyn share an overlapping dosage form (injection). However, the total dose given as a single injection differs since the dose of Amikin will be calculated based on the patient's weight, while the dose of Apokyn will not be ordered in strengths greater than 10 mg for each individual dose. The dosing regimen differs as well. Amikin is given two or three times daily while Apokyn is given up to 5 times daily. Although some similarities exist between the two products, the aforementioned differences coupled with phonetic distinctions ("-mi-" vs "-po-") help differentiate the two products and lessen the concern for confusion.

- 4 Aphrodyne has sound-alike potential with the proposed proprietary name Apokyn. Aphrodyne is an indolalkylamine alkaloid reviewed under the Drug Efficacy Study Implementation (DESI) project and it is regarded as ineffective for any indication. Unlabeled uses include impotence and orthostatic hypotension. The prefixes "Aph-" vs "Ap-" sound similar and the suffixes "-yne" vs "-yn" can sound similar if the "-yne" is pronounced as IN. However, if spoken with a long vowel sound, the suffixes sound somewhat different. Differences in the body of the names, "-rod-" in Aphrodyne vs "-ok-" in Apokyn, differentiate the two names from one another. Differences between Aphrodyne and Apokyn include dosing regimen (three times daily vs multiple times a day), dose (5.4 mg vs 2mg to 10 mg), dosage form (oral tablet vs injection), route of administration (oral vs subcutaneous). Given the differences between the two products, the likelihood for confusion between the two drugs is minimal.

- 5 Aprodine and Apokyn have some sound-alike characteristics. Aprodine, an over-the-counter (OTC) drug product, contains pseudoephedrine hydrochloride and triprolidine hydrochloride and is indicated as a decongestant and antihistamine. Aprodine is available as a 60 mg/2.5 mg tablet. The prefixes "Apro-" vs "Apo-" are similar in sound and the suffixes "-ine" vs "-yn" can sound similar if the "-ine" in Aprodine is pronounced as IN. The middle sound "-d-" in Aprodine vs the "-k-" sound in Apokyn phonetically distinguish one name from the other. The products differ with respect to many other characteristics including dosage form (tablet vs injection), route of administration (oral vs subcutaneous), and strength (60 mg/2.5 mg vs 10 mg/mL). Although a prescription for Aprodine may not be prescribed with a strength, a prescription for Apokyn must indicate a dose ranging from 2 mg to 10 mg which will not overlap with a dose used for Aprodine. Additionally, the Rx/OTC status may further minimize any confusion caused between the two drug names.

- 6 Capoten and Apokyn were identified as having sound-alike and look-alike potential. Capoten, an angiotensin-converting enzyme (ACE) inhibitor, is indicated for the treatment of hypertension, congestive heart failure, and to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction. Capoten and Apokyn share the letters "-apo-" vs "Apo-" and have similar sounding suffixes, "-oten" vs "-okyn". The "-oten" vs "-okyn" owe their similarity to the leading

short "o" followed by a hard consonant, however, the "C" in Capoten helps differentiate the two product names from one another. Likewise, although the two drug products have overlapping orthographic characteristics ("Ca-" resembles the "A-" in Apokyn (see below) and "-pot-" looks like "-pok-"), the downstroke of the "-y-" in Apokyn distinguishes the two names from each other. The products differ in strength (12.5 mg, 25 mg, 50 mg, and 100 mg vs. 10 mg/mL), dosage form (tablet vs. injection), and route of administration (oral vs. subcutaneous). Given the differences in the aforementioned characteristics, the risk of confusion between the two names is minimal.

Capoten Apokyn

E STUDY AND ANALYSIS

("Market Research for Proposed Name "Apokyn" dated July 22, 2003)

_____ conducted a study to evaluate the potential for error between Apokyn and currently marketed brand/generic drug products. The _____ reported that 100 physicians and 100 pharmacists participated in the study. The specialties of the physicians and pharmacists were Neurologists (70), Internal Medicine Physicians (20), Primary Care Physicians and Family Practice Physicians (10), Institution-based pharmacists (50) and Community pharmacists (50). The response rate was 34% for physician nomenclature review and prescription collection and 37% for prescription interpretation study and pharmacist nomenclature review. The medical professionals participated in various aspects of the three phases of the _____ study. The four sections of the study as well as study findings are discussed below.

1 Section A – Physician Nomenclature Review and Prescription Collection

_____ asked 100 physicians to view the test name, Apokyn, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined if Apokyn had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims." Verbal and handwritten prescriptions of the proposed proprietary name were collected from these physicians to be used in Section B of the study. The physicians provided oral and handwritten interpretations of the following Apokyn prescription:

*Apokyn
1 unit
Inject SQ 1 mg PRN*

DMETS Response

Although _____ indicates that 295 physicians were asked to participate in this phase of the study, the response rate was only 34% (100 physicians). _____ notes that this is a "typical" response rate for a survey of this type. However, there are limitations in the predicative value of these studies, primarily due to the sample size. It is not indicative as to what will occur once the drug is widely prescribed.

Physicians were requested to identify any hyperbole or false claims implied by Apokyn — reports that none of the physicians polled had an issue with the name from the perspective of promotion Physicians were also requested to identify medical terms or devices that had sound-alike or look-alike properties to Apokyn, and to identify any existing names they considered to be similar to Apokyn based on sound, appearance, or both DMETS concurs with the — assessment that the three proprietary/established names identified by the physicians (*Dextran, Zosyn, and Epogen*) have a low potential for confusion with Apokyn The medical terms (*Apocrine, Apoptosis, Apoxia*) identified by — should not present confusion for the name Apokyn since the context for use would lessen the potential for errors DMETS concurs with the — assessment that the word “apocrine” nor the other terms identified pose an apparent issue for prescribing/dispensing of Apokyn

2 Section B – Prescription Interpretation Study and Pharmacist Nomenclature Review

— provided 50 actively practicing pharmacists (25 community and 25 institution-based) with a verbal prescription for Apokyn and another group of fifty pharmacists (25 community and 25 institution-based) with a written prescription for Apokyn The objective of this phase is to determine if any of the sample Apokyn prescriptions would be interpreted as a currently marketed brand or established name product Additionally, — asked 100 pharmacists to view the test name, Apokyn, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance They also determined if Apokyn had sound-alike or look-alike properties to any medical terms or devices The participants evaluated the proposed name for any relationship to “hyperbole or false claims” All of the respondents correctly identified the name Apokyn from verbal and handwritten prescriptions

DMETS Response

— reports that 50 (100%) of the pharmacists interpreted the verbal prescription correctly, and 50 (100%) of the pharmacists interpreted the handwritten prescription correctly As noted with the physician response rate, — indicated that the response rate in this portion of the study was 37% (100 pharmacists) Again, there are limitations in the predictive value of these studies, primarily due to the sample size It is not indicative as to what will occur once the drug is widely prescribed Pharmacists were requested to identify any hyperbole or false claims implied by Apokyn None of the pharmacists polled had an issue with the name from the perspective of promotion Pharmacists were also requested to identify medical terms or devices that had sound-alike or look-alike properties to Apokyn, and to identify any existing names they considered to be similar to Apokyn based on sound, appearance, or both Five medical terms were indicated as having similarity to the proposed name They were apocrine, apogamy, apoptosis, kinesis, and kinetic There were four proprietary/established names that were identified as being similar to the proposed name Apokyn (*Aprotinin, Epogen, Asendin, and Zosyn*) DMETS concurs with the — assessment that the four proprietary names identified by the pharmacists have a low potential for confusion with Apokyn

3 Computer-Assisted Analysis

— conducted a “comprehensive search of medical references” to identify brand and established name products that may sound-alike or look-alike to the proposed name Apokyn. Fourteen names were compared to Apokyn using — database and using a “Phonological and Orthographical Similarity Analysis”. The “Phonological and Orthographical Similarity Analysis” identifies a threshold of similarity between Apokyn and the products identified during the search of the medical references. The objective of this analysis is to identify the ‘similarity between the proposed proprietary name and any sound-alike or look-alike product’. The proprietary name Apokyn exceeded the threshold value for the Phonologic Similarity Ratio, a measure of sound-alike similarity, when compared to —

— Additionally, — conducted a search of medical reference materials for medical terms, acronyms, and abbreviations similar to Apokyn, including medical terms mentioned by physicians in Section A and pharmacists in Section B of the study.

DMETS Response

DMETS agrees with — that although — exceeded the threshold value for Phonologic Similarity Ratio measurements, overall, this product has minimal common features when compared with the profile of Apokyn. — identified 18 medical terms, abbreviations, and acronyms that were similar to the proposed name. These were *Apocrine, Apogamy, Apolipoproteins, Apollo 95E tooth-whitening and curing system, Apomate™, Apoplexy, Apoptosis, Aproxia, Kinesis, Kinetic, APO (Acquired pendular oscillation), APO (Adriamycin), APO (Adverse patient occurrence), APO (Adverse Pregnancy Outcomes), APO (Apolipoprotein), APO (Apoprotein), APO (Apoptosis), and KYN (Kynurenic Acid)*. DMETS concurs with — assessment that these medical terms, acronyms, and abbreviations pose no apparent safety issue for prescribing and dispensing of Apokyn.

4 Pharmacists’ Analysis – Professional Review Committee (PRC)

Five actively practicing community and institution-based pharmacists provided an independent analysis of the proposed proprietary name, Apokyn, by considering its potential for error and potential for patient harm in the event of an error. The pharmacists were provided with the product concept and profile information for Apokyn, as well as research data from all sections of the study, and were asked to evaluate this information. The pharmacists evaluated all of the data obtained during this study. The PRC also considered recommendations for safe medication practices and pharmacy procedures, postings by FDA MedWatch, Newsletters and Medication Safety Alerts from the Institute for Safe Medication Practices, postmarketing surveillance information including errors and adverse events as reported in the National Coordinating Council for Medication Error Reporting and Prevention website, U.S. Pharmacopoeia website, the U.S. Pharmacopoeia Quality Review – Stop, Look, and Listen! List, and the American

Drug Index Monograph "Drug Names That Look Alike and Sound Alike" The board also stated that the study findings regarding the evaluation of hyperbole and fanciful claims indicated nothing misleading or inappropriate about the proposed proprietary name Therefore, Apokyn should be considered an appropriate proprietary name

DMETS Response

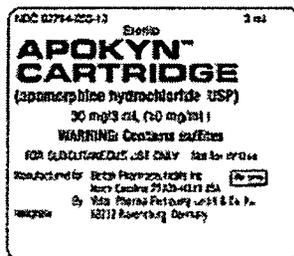
DMETS agrees with the board's conclusion that overall, the proposed proprietary name Apokyn is acceptable from a safety perspective

III LABELING, PACKAGING , AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Apokyn, DMETS has attempted to focus on safety issues relating to possible medication errors DMETS has identified several areas of possible improvement, which might minimize potential user error

A GENERAL COMMENTS

- 1 The terminology "units", "cc", and "mL" are used interchangeably throughout the container labels, carton and insert labeling To minimize potential confusion, a single term should be used consistently throughout the literature
- 2 DMETS is concerned with the proposed cartridge packaging configuration The container label and carton labeling does not clearly state that the Apokyn cartridge must ONLY be used with the Apokyn Pen Pak The Apokyn cartridge resembles other currently marketed cartridges which can be administered intravenously Apokyn can only be administered subcutaneously due to the serious adverse events (such as intravenous crystallization of apomorphine, leading to thrombus formations and pulmonary embolism) following intravenous use of apomorphine DMETS is concerned about a potential drug misadventure, should the user attach the cartridge to another device (e g tubex injector) and inject the Apokyn cartridge intravenously Please assure that a needle cannot be attached or that this cartridge can not be delivered via a needleless system We recommend including a statement on the cartridge container label and carton labeling which clearly states that the Apokyn cartridge must ONLY be used with the Apokyn Pen Pak In addition, we recommend including a statement which indicates that the device must only be used subcutaneously



- 3 The carton label for the Apokyn Pen Pak indicates in prominent letters that it is "For use with Apokyn 3 mL Cartridges (see below) Users could potentially be misled to believe that the cartridges will be included in the Pen Pak contents DMETS recommends moving the description "3 mL Cartridges" from the second line to the first line, immediately following "For Use With APOKYN" Additionally, we recommend deleting the established name for this product does not contain any drug

NDC 0234-253-04

APOKYN™ PEN PAK

For Use With APOKYN™
(apomorphine hydrochloride, USP) 3 mL Cartridges

Contents: One APOKYN™ Pen, Six BD Ultra-Fine™ Pen Needles,
One Carrying Case, One Information For Use Booklet.



B CONTAINER LABEL (Ampule and Cartridge)

- 4 See GENERAL COMMENTS
- 5 We recommend that the established name be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10(g)(2)
- 6 Increase the prominence of the product strength
- 7 We were unable to compare the two different label designs (ampule vs cartridge) with the black and white copies that were provided Please ensure the labels and labeling are clearly differentiated using contrasting colors, boxing, or some other means
- 8 DMETS recommends
- 9 The "AMPULE" and "CARTRIDGE" statements appear in capital letters on the principal display panel adjacent to or immediately below the proprietary name DMETS recommends that this statement be deleted or placed with less prominence so that it does not interfere with the readability of the proprietary name For example **APOKYN™ Ampule** If the descriptors "ampule" and "cartridge" are deleted, we recommend revising "2 mL" to "2 mL ampule" and "3 mL" to "3 mL cartridge"
- 10 Include the dosage form with the established name For example

APOKYN™
(Apomorphine Hydrochloride Injection)
20 mg/2 mL (10 mg/mL)

B CARTON LABELING

See GENERAL COMMENTS and B3, B4, B6, and B7 comments

C INSERT LABELING and INSTRUCTIONS FOR USE LABELING

- 1 See A1 comment
- 2 Eliminate terminal zeros in the expressions of strength throughout labels and labeling (e g 1 cc instead of 1 0 cc)

3 INDICATIONS AND USAGE

a DMETS notes



**APPEARS THIS WAY
ON ORIGINAL**

IV RECOMMENDATIONS

- A DMETS has no objections to the use of the proposed proprietary name, Apokyn This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document
- B DMETS recommends the labeling revisions as outlined in section III of this review that might lead to a safer use of this product We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer
- C DDMAC finds the proprietary name Apokyn acceptable from a promotional perspective

DMETS would appreciate feedback of the final outcome of this consult We would be willing to meet with the Division for further discussion, if needed If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242

/s/

Jinhee L Jahng, Pharm D
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur

/s/

Alina Mahmud, R Ph
Team Leader
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/s/

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COMPLETED SEP 19 2003

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date August 26, 2003

To Russell Katz, M D , Director
Division of Neuropharmacological Drug Products (HFD-120)

Through Deborah B. Leiderman, M D , Director /S/
Michael Klein, Ph D , Team Leader /S/
Controlled Substance Staff (HFD-009)

From Katherine Bonson, Ph D , Pharmacologist /S/
Controlled Substance Staff (HFD-009)

Subject Consult reviewing clinical abuse potential protocol
NDA 21-264
Apomorphine
Treatment for Parkinson's Disease
Sponsor Bertek Pharmaceuticals, Inc

Background

CSS was consulted by HFD-120 on the abuse potential of the dopamine agonist apomorphine (NDA 21-264), which is used for L

1

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Apomorphine is approved in the UK for PD (as Britaject) and in Europe for erectile dysfunction (as Uprima) There are currently no marketed apomorphine drug products in the US

The medical officer in HFD-120 noted that the Integrated Summary of Safety (ISS) cited four case reports from the medical literature of men with PD who received apomorphine and subsequently became hypersexual None of these individuals participated in clinical

studies conducted under the Sponsor's IND. These sexual responses led to outright drug seeking and non-therapeutic dose-escalation. Each of the four patients self-administered excessively high daily doses of apomorphine, resulting in a preoccupation with masturbation and socially inappropriate sexual advances towards their wives or other women. HFD-120 requested comments from CSS regarding the need for additional investigation of this phenomenon.

Conclusions

* CSS review of the ISS revealed that out of 516 PD patients who received apomorphine, 3 patients had emergent changes in libido (2 increased, 1 decreased) and 8 male patients had an increase in erections (including priapism). The majority of these subjects (n = 488) were run in an open-label study in patients with advanced PD, without a comparison placebo group. There were no reported cases of patients engaged in drug-seeking or non-therapeutic dose-escalation for the purpose of increasing sexual effects. In one of the priapism cases, the patient chose to drop out of the study, demonstrating that sexual side effects did not lead to drug-seeking.

* The ability of apomorphine to physiologically induce sexual side effects is well known, as evidenced by its approval in Europe for the treatment of erectile dysfunction under the name Uprima.

* No abuse potential studies have been conducted in humans with apomorphine. However, it is unlikely that apomorphine would be abused by healthy individuals for psychic effects because of the well-known emetic response at doses that produce CNS stimulation. The Drug Abuse Warning Network database does not list apomorphine among abused drugs.

* In the NDA review, HFD-120 suggests that "attempts to avoid all symptoms of all "Off" events when "Off" events occur frequently" could be characterized as "drug abuse". This interpretation is not consistent with the standard definition of drug abuse. Drug abuse is characterized by compulsive use of a drug for psychic effects, or continued use of that drug for psychic effects despite untoward consequences. The medical use of a drug by patients to ameliorate symptoms resulting from a disease is not characterized as drug abuse.

Recommendation

* Linkage between hypersexual responses from apomorphine and drug abuse has not been demonstrated. However, it may be appropriate to include a warning in the apomorphine label regarding the possibility of hypersexual responses or dose escalation for the purpose of enhancing sexual effects in PD patients.

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/s/

Joseph Salewski

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MEMORANDUM OF TELECON

DATE August 7, 2003

APPLICATION NUMBER NDA 21-264 **Apomorphine Injection**

BETWEEN

Name Andrea Miller
Dr O'Donnell
Dr Bottini
Dr Van Loom
Dr Smith
Dr Shaw
Phone (301) 594-6649
Representing **Bertek Pharmaceuticals**

AND

Division of Neuropharmacological Drug Products, HFD-120
Name Dr Katz - Division Director
Dr Feeney – Group Leader
Dr Kapcala – Medical Reviewer
Dr Freed – Pharmacology Team Leader
Dr Roney – Pharmacology Reviewer
Dr Uppoor – Clinical Pharmacology & Biopharmaceutics Team Leader
Dr Duan – Clinical Pharmacology & Biopharmaceutics Reviewer
CDR Teresa Wheelous – Sr Regulatory Management Officer

SUBJECT Timing of Mass Balance Studies Requested in the Approvable Letter

BACKGROUND

In a July 11, 2003 submission, the sponsor requested a telecon to discuss the Toxicology and Clinical Pharmacology requests for mass balance studies prior to approval as stated in the Agency's July 2, 2003 approvable letter Bertek Pharmaceuticals provided posters along with an argument in an August 1, 2003 submission in support of their position to conduct the mass balance study post approval

Additionally, this August 1, 2003 submission requested guidance on (1) the Agency's acceptance of an algorithm to use in defining a specific off as either an end-of-dose or a spontaneous off, and (2) acceptance of December 31, 2002 as the new cut-off date for the safety update and June 30, 2003 as the cut-off date for serious adverse events

DISCUSSION

Mass Balance Study

- Bertek stated that the completion of the mass balance study would be from 6- 9 months in total Six to 12 weeks is required to develop the isotope and about 6 months to conduct the study