

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR.**

**APPLICATION NUMBER**

**21-264**

**Chemistry Review(s)**

# **NDA 21-264**

**APOKYN™ (apomorphine hydrochloride) Injection  
10 mg/mL**

**BERTEK Pharmaceuticals Inc.**

**Thomas A. Broadbent, Ph.D.  
Division of Neuropharmacological Drug Products**

# Table of Contents

<b>Chemistry Review Data Sheet</b>	<b>5</b>
<b>The Executive Summary</b>	<b>.9</b>
I Recommendations	9
A Recommendation and Conclusion on Approvability	9
B Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps	9
II Summary of Chemistry Assessments	9
A Description of the Drug Product and Drug Substance	9
B Description of How the Drug Product is Intended to be Used	10
C Basis for Approvability or Not-Approval Recommendation	10
III Administrative	11
A Reviewer's Signature	11
B Endorsement Block	11
C CC Block	11
<b>Chemistry Assessment</b>	<b>12</b>
<u>Response to Deficiencies</u>	
Drug Substance	12
A Description	12
B Impurities	12
C Residual Solvents	12
D Heavy Metals	13
E Chiral Assay	13
Drug Product	
A Composition/Components	13
B 1 Specifications (Sampling)	14
B 2 Specifications (Description)	14
B 3 Specifications (Impurity Limits)	14
B 4 Specifications (Impurity Structures)	14
C 1 Stability (Expiration Period)	15
C 2 Stability (Shelf-life Specifications)	15

<b>Establishment Inspection</b>	<b>15</b>
<b>Labeling</b>	
A Proprietary Name	15
B 1 Package Insert (Systematic Name)	16
B 2 Package Insert (Spelling)	16
B 3 Package Insert (Storage Statement)	16
C Container Labels	16
<b><u>Review Notes</u></b>	
<b>A Drug Substance</b>	<b>17</b>
1 Description and Characterization	17
2 Manufacturer	17
3 Synthesis / Method of Manufacture	17
4 Process Control	17
<b>A 6 Regulatory Specifications / Analytical Methods</b>	<b>17</b>
A Drug Substance Specifications and Tests	17
B Purity Profile	18
C Microbiology	18
<b>A 7 Container/Closure System for Drug Substance Storage</b>	<b>18</b>
<b>A 8 Drug Substance Stability</b>	<b>18</b>
<b>B Drug Product</b>	<b>19</b>
1/2 Components/Composition	19
<b>B 3 Specifications and Methods for Drug Product Ingredients</b>	<b>19</b>
<b>B 4 Manufacturer</b>	<b>19</b>
<b>B 5 Methods of Manufacturing and Packaging</b>	<b>20</b>
A Production Operations	20
B In-process Controls and Tests	21
C Reprocessing Operations	21
<b>B 6 Regulatory Specifications and Methods for Drug Product</b>	<b>22</b>
A Sampling Procedures	22
B Regulatory Specifications and Methods	23
C Batch Analysis	25
<b>B 7 Container/Closure System</b>	<b>25</b>

B 8 Microbiology	25
B 9 Drug Product Stability	26
C Investigational Formulations	27
D Environmental Assessment	27
E Methods Validation	27
F Labeling	28
G Establishment Inspection	36
Attachment 1 (Tabular Summary of Drug Substance Specifications)	43

**APPEARS THIS WAY  
ON ORIGINAL**

# Chemistry Review Data Sheet

- 1 NDA 21-264
- 2 REVIEW # 2
- 3 REVIEW DATE 04-MAR-2004
- 4 REVIEWER Thomas A Broadbent, Ph D
- 5 PREVIOUS DOCUMENTS

<u>Previous Documents</u>	<u>Document Date</u>
Telecon (DMF) —	05-MAR-2003
Telecon	27-MAY-2003
Telecon (DMF) >	04-JUN-2003
Telecon (DMF) —	06-JUN-2003
Telecon	12-JUN-2003
Telecon	03-MAR-2004
CMC Review # 1	13-JUN-2003

6 SUBMISSIONS BEING REVIEWED

<u>Submissions Reviewed</u>	<u>Document Date</u>
Amendment BZ	16-JUN-2003
Amendment BC	19-JUN-2003
Amendment BC	25-JUN-2003
New Correspondence	02-JUL-2003
Amendment AZ	17-OCT-2003
Amendment BC	02-MAR-2004

7 NAME & ADDRESS OF APPLICANT

Name	BERTEK Pharmaceuticals Inc
Address	P O Box 4310, 781 Chestnut Ridge Road Morgantown WV, 26504-4310
Representative	Andrea B Miller, R Ph , Esq
Telephone	(304) 599-2595

**8 DRUG PRODUCT NAME/CODE/TYPE**

- a) Proprietary Name APOKYN™
- b) Non-Proprietary Name (USAN) Apomorphine Hydrochloride
- c) Code Name/# N/A
- d) Chem Type/Submission Priority
  - Chem Type = 1
  - Submission Priority = P

**9 LEGAL BASIS FOR SUBMISSION**

N/A

**10 PHARMACOL CATEGORY**

Dopamine receptor agonist / Therapy of acute refractory episodes of immobility or hypomobility in late stage Parkinson's disease

**11 DOSAGE FORM Sterile Solution for Injection**

**12 STRENGTH/POTENCY 10 mg/mL**

**13 ROUTE OF ADMINISTRATION Subcutaneous Injection**

**14 Rx/OTC DISPENSED YES Rx      OTC**

**15 SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)**

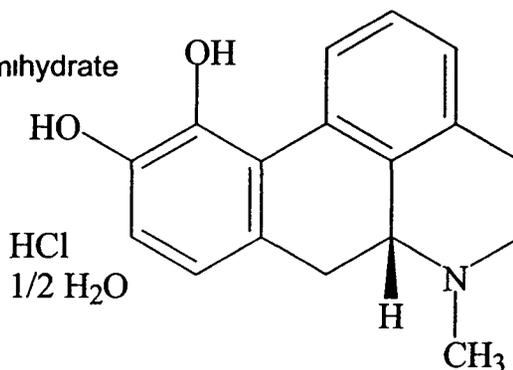
     SPOTS product – Form Completed  
  X   Not a SPOTS product

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

6aβ-Aporphine-10,11-diol hydrochloride hemihydrate

C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub> • HCl • ½H<sub>2</sub>O  
 Formula Weight 312.79

CAS Reg # [41372-20-7]  
 (hemihydrate)



**17 RELATED / SUPPORTING DOCUMENTS**

**A DMFs**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	2	—	Apomorphine HCl	1	Inadequate Adequate	4 Feb 2003 11 June 2003	Drug substance
—	2	—	Apomorphine HCl	1	Adequate	11 June 2003	Drug substance
—	3	—	—	1	Adequate	19 Feb 2003	—
—	3	—	—	1	Adequate	27 Dec 2002	—
—	3	—	—	1	Adequate	22 April 2002	—
—	3	—	—	4	N/A	—	—

<sup>1</sup> Action codes for DMF Table

1 – DMF Reviewed

Other codes indicate why the DMF was not reviewed as follows

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate Inadequate, or N/A (There is enough data in the application therefore the DMF did not need to be reviewed)

**B Other Documents**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
—	—	Pen injector, Beckton Dickinson
IND	52,844	Product Development, Mylan Pharm

**APPEARS THIS WAY  
ON ORIGINAL**

**18 STATUS**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
CDRH	Pen injector acceptable	21-MAY-2003	Von Nakayama
EES	Acceptable	25-SEP-2003	S Adams
Pharm/Tox	Not Approvable Not Approvable	17-JUN-2003 27-JUN-2003	Paul Roney Lois Freed
Biopharm	Approval with Phase 4 commitment	24-JUN-2003 11-AUG-2003	John Duan John Duan
LNC	Not applicable	N/A	--
Methods Validation	Adequate (PHI-DO) Pending (DPA)	17-DEC-2003 --	Elise Murphy --
ODS / DMETS	unacceptable Not Recommended No objection to "Apokyn"	13-AUG-2002 07-MAR-2003 16-DEC-2003	Marcy Ann Lee Alina Mahmud Jinhee Jahng
ODS / DSRCS	Recommended various changes to the Patient Information Insert (instructions for use of the ampules and injector pen)	18-FEB-2004	Janine Best
EA	Waiver acceptable	10-APR-2003	Florian Zielinski
Microbiology	Approvable Approval	31-MAR-2003 12-MAY-2003	Steven Langille Steven Langille

**APPEARS THIS WAY  
ON ORIGINAL**

# The Chemistry Review for NDA 21-264

## The Executive Summary

### I Recommendations

#### A Recommendation and Conclusion on Approvability

Recommend Approval of NDA 21-264

#### B Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II Summary of Chemistry Assessments

#### A Description of the Drug Product and Drug Substance

##### Drug Substance

Apomorphine hydrochloride is a white to gray-white crystalline powder. The semi-synthetic drug substance and compendial article (USP, BP & Eur Ph) is provided as the hemihydrate (see formula). The substance is [redacted] two manufacturers, [redacted] (DMF [redacted] and [redacted] (DMF [redacted]). It is a chiral compound with one stereogenic center at the 6a atom (see structure). The stereogenic center is retained from the [redacted] the starting material. The absolute configuration is [redacted] with the specific rotation  $-60.5$  to  $-63.0^\circ$ . Crystal form, particle size and level of hydration are not relevant to this application as the drug product is a solution. The limit of aqueous solubility is [redacted]. Manufacturing process impurities include [redacted]. Two degradation products that can form in the drug substance (and product) are [redacted]. The [redacted] degradation products are [redacted] readily detected by visual inspection and the USP Color Test in the drug substance specifications. The drug substance is stable and does not become discolored when stored in sealed containers.

**APPEARS THIS WAY  
ON ORIGINAL**

Executive Summary Section

Drug Product

The names, \_\_\_\_\_ proposed during the first review cycle, were not accepted by the Division of Medical Errors and Technical Support (DMETS) DMETS has no objections to the currently proposed proprietary name, Apokyn™ The drug product is a sterile, clear, aqueous solution of apomorphine hydrochloride, USP, 10 mg/mL It is almost colorless when first manufactured, but may become colored with age The solution is formulated with sodium metabisulfite, NF, 1 mg/mL, \_\_\_\_\_ The bisulfite ion in solution \_\_\_\_\_ degradation products The solution is also formulated with sodium hydroxide, NF, and/or hydrochloric acid, NF, to adjust the pH of the product as necessary The product is packaged in ampules of \_\_\_\_\_ glass The ampules are filled to 2 mL This formulation is identical to Britaject® Injection, which is manufactured, approved and distributed in the United Kingdom Another presentation of the drug product is a cartridge of \_\_\_\_\_ glass and \_\_\_\_\_ rubber The fill volume of the cartridge is 3 mL The cartridge formulation contains 5 mg/mL of benzyl alcohol \_\_\_\_\_ in addition to the ingredients described above The cartridge is to be used with the Becton Dickinson injector-pen (BDPS Pen II) for multi-dose administration, which has been found acceptable by CDRH consult The sponsor has requested 24 months expiration dating for the ampule configuration and 18 months expiration dating for the cartridge configuration (request of resubmission) Expiration dating of 24 months was justified for the ampule product in the first review cycle Expiration dating of 18 months was justified for the cartridge product in the second review cycle

**B Description of How the Drug Product is Intended to be Used**

The drug product \_\_\_\_\_ It is indicated for subcutaneous administration only The starting dose to treat episodes of immobility is 2 mg Preparatory and concomitant administration of trimethobenzamide (antiemetic) is recommended because of nausea that can be induced by apomorphine The dose is titrated in 1 mg increments Caution is recommended for doses above 6 mg Instructions are provided to prepare syringes from the ampule and for the manner of injection Separate instructions are provided for the multiple-use Becton Dickinson delivery pen used with the cartridge Both the 2 mL ampules and the 3 mL cartridges are provided in cartons of five

**C Basis for Approvability or Not-Approval Recommendation**

Approval is recommended All CMC deficiencies identified in the first review have been adequately addressed

APPEARS THIS WAY  
ON ORIGINAL

**III Administrative**

**A Reviewer's Signature**

In Division File System

**B Endorsement Block**

In Division File System

**C CC Block**

Thomas Broadbent, CMC Reviewer  
Maryla Guzewska, CMC Team Leader  
John Simmons, DNDC1 Division Director  
Hasmukh Patel, DNDC1 Deputy Division Director  
Teresa Wheelous, Project Manager

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ON ORIGINAL**

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Thomas Broadbent  
3/9/04 02 23 25 PM  
CHEMIST

Added tabular summary of DS specifications

Maryla Guzewska  
3/9/04 03 04 36 PM  
CHEMIST

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CHEMIST

initialled 6/17/2003

Maryla Guzewska  
6/17/03 10 15 41 AM  
CHEMIST

# **NDA 21-264**

## **[Tradename] (apomorphine hydrochloride) Injection 10 mg/mL**

— the current name, will be replaced by a proprietary name yet to be determined)

**BERTEK Pharmaceuticals Inc.**

**Thomas A. Broadbent, Ph.D.  
Division of Neuropharmacological Drug Products**



# Table of Contents

<b>Chemistry Review Data Sheet</b>	..	.	<b>4</b>
<b>The Executive Summary</b>	.	.	<b>..7</b>
I Recommendations			7
A Recommendation and Conclusion on Approvability			7
B Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable			7
II Summary of Chemistry Assessments			7
A Description of the Drug Product(s) and Drug Substance(s)			7
B Description of How the Drug Product is Intended to be Used			8
C Basis for Approvability or Not-Approval Recommendation			8
III Administrative			9
A Reviewer s Signature			9
B Endorsement Block			9
C CC Block			9
<b>Chemistry Assessment</b>			<b>10</b>
A DRUG SUBSTANCE			10
1 Description & Characterization			10
a Description			10
b Characterization / Proof of Structure			10
2 Manufacturer			10
3 Synthesis / Method of Manufacture			11
a Starting Materials - Specs & Tests			11
b Solvents Reagents etc			11
c Flow Chart			11
d Detailed Description			11
4 Process Controls			12
5 Reference Standard			12
6 Regulatory Specifications / Analytical Methods			12
a Drug Substance Specifications & Tests			12

b Purity Profile	16
c Microbiology	17
7 Container/Closure System for Drug Substance Storage	17
8 Drug Substance Stability	18
<b>B DRUG PRODUCT</b>	<b>18</b>
1 Components / 2 Composition	19
3 Specifications & Methods for Drug Product Ingredients	20
a Active Ingredient	20
b Inactive Ingredients	20
4 Manufacturer	21
5 Methods of Manufacturing and Packaging	23
a Production Operations	23
b In-Process Controls & Tests	25
c Reprocessing Operations	25
6 Regulatory Specifications and Methods for Drug Product	26
a Sampling Procedures	26
b Regulatory Specifications and Methods	26
c Batch Analysis	32
7 Container/Closure System	34
8 Microbiology	36
9 Drug Product Stability	37
<b>C INVESTIGATIONAL FORMULATIONS</b>	<b>40</b>
<b>D ENVIRONMENTAL ASSESSMENT</b>	<b>41</b>
<b>E METHODS VALIDATION</b>	<b>41</b>
<b>F LABELING</b>	<b>42</b>
<b>G ESTABLISHMENT INSPECTION</b>	<b>47</b>
<b>DRAFT DEFICIENCIES</b>	<b>53</b>



# Chemistry Review Data Sheet

- 1 NDA 21-264
- 2 REVIEW # 1
- 3 REVIEW DATE 13-JUN-2003
- 4 REVIEWER Thomas A Broadbent
- 5 PREVIOUS DOCUMENTS

<u>Previous Documents</u>	<u>Document Date</u>
Telecon (DMF) —	05-MAR-2003
Telecon	27-MAY-2003
Telecon (DMF) —	04-JUN-2003
Telecon (DMF) —	06-JUN-2003
Telecon	12-JUN-2003

## 6 SUBMISSIONS BEING REVIEWED

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
ORIGINAL	14-JUN-2002
Amendment	17-SEP-2002
Amendment	17-APR-2003
Amendment	28-APR-2003

## 7 NAME & ADDRESS OF APPLICANT

Name	BERTEK Pharmaceuticals Inc
Address	P O Box 4310, 781 Chestnut Ridge Road Morgantown WV, 26504-4310
Representative	Andrea B Miller, R Ph Esq
Telephone	(304) 599-2595

### 8 DRUG PRODUCT NAME/CODE/TYPE

- a) Proprietary Name Yet to be determined — is the latest name provided
- b) Non-Proprietary Name (USAN) Apomorphine Hydrochloride, USP
- c) Code Name/# N/A
- d) Chem Type/Submission Priority
  - Chem Type = 1
  - Submission Priority = P

### 9 LEGAL BASIS FOR SUBMISSION

N/A

### 10 PHARMACOL CATEGORY

Dopamine receptor agonist / Therapy of acute refractory episodes of immobility or hypomobility in late stage Parkinson s disease

### 11 DOSAGE FORM Sterile Solution for Injection

### 12 STRENGTH/POTENCY 10 mg/mL

### 13 ROUTE OF ADMINISTRATION Subcutaneous Injection

### 14 Rx/OTC DISPENSED YES Rx     OTC

### 15 SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

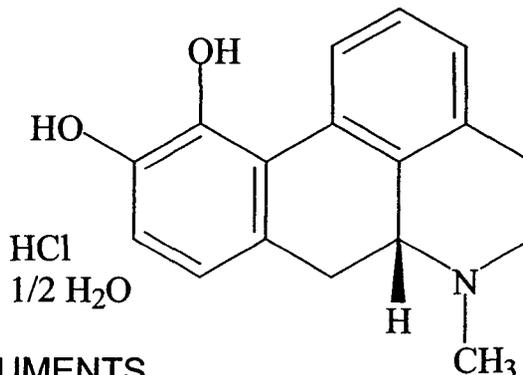
SPOTS product – Form Completed  
 Not a SPOTS product

### 16 CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

6aβ-Aporphine-10 11-diol hydrochloride hemihydrate

C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub> • HCl • ½H<sub>2</sub>O  
 Formula Weight 312.79

CAS Reg # [41372-20-7]  
 (hemihydrate)



### 17 RELATED / SUPPORTING DOCUMENTS

**A DMFs**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE 1	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS

# CHEMISTRY REVIEW

## Executive Summary Section

2	Apomorphine HCl	1	Inadequate	4 Feb 2003	Drug substance
2	Apomorphine HCl	1	Adequate	11 June 2003	Drug substance
3		1	Adequate	19 Feb 2003	
3		1	Adequate	27 Dec 2002	
3		1	Adequate	22 April 2002	
3		4	N/A	--	

<sup>1</sup> Action codes for DMF Table

1 – DMF Reviewed

Other codes indicate why the DMF was not reviewed, as follows

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate Inadequate or N/A (There is enough data in the application therefore the DMF did not need to be reviewed)

### B Other Documents

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		Pen injector, Beckton Dickinson
IND	52 844	Product Development, Mylan Pharm

## 18 STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CDRH	Pen injector acceptable	21-MAY-2003	Von Nakayama
EES	Pending OC recomment	--	Tom Broadbent
Pharm/Tox	Pending	--	Paul Roney
Biopharm	Pending	--	John Duan
LNC	Not applicable	N/A	--
Methods Validation	Pending submission to Agency laboratory	--	Thomas Broadbent
ODS / DMETS	unacceptable Not Recommended	13-AUG-2002 07-MAR-2003	Marcy Ann Lee Alina Mahmud
EA	Waiver acceptable	N/A	Florian Zielinski
Microbiology	Approvable Approval	31-MAR-2003 12-MAY-2003	Steven Langille

# The Chemistry Review for NDA 21-264

## The Executive Summary

### I. Recommendations

#### A Recommendation and Conclusion on Approvability

Recommend NDA 21-264 as approvable from the CMC perspective. Before this application may be approved, it will be necessary to address all deficiencies listed on pages 53 and 54.

#### B Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II Summary of Chemistry Assessments

#### A Description of the Drug Product and Drug Substance

##### Drug Substance

Apomorphine hydrochloride is a white to gray-white crystalline powder. The drug substance and compendial article (USP, BP & Eur Ph) is provided as the hemihydrate (see formula). It is a chiral compound with one stereogenic center at the 6a atom (see structure). The absolute configuration is with the specific rotation  $-60.5$  to  $-63.0^\circ$ . Crystal form, particle size and level of hydration are not relevant to this application as the drug product is a solution. The limit of aqueous solubility is. The substance is

manufacturers,

(DMF) and

(DMF)

two

Manufacturing process impurities

Two

degradation products that can form in the drug substance (and product) are

are readily detected by visual inspection and the USP Color Test in the drug substance specifications. The drug substance is stable and does not become discolored when stored in sealed containers.

**APPEARS THIS WAY  
ON ORIGINAL**

**Drug Product**

The proposed names of the drug product, \_\_\_\_\_, were not accepted by DMETS. The drug product is a sterile, clear, aqueous solution of apomorphine hydrochloride, USP, 10 mg/mL. It is almost colorless when first manufactured, but may become colored with age. The solution is formulated with sodium metabisulfite, NF, 1 mg/mL,

The solution is also formulated with sodium hydroxide, NF, and/or hydrochloric acid, NF, to adjust the pH of the product as necessary. The product is packaged in ampules of \_\_\_\_\_ glass. The ampules are filled to 2 mL. This formulation is identical to Britaject® Injection, which is manufactured, approved and distributed in the United Kingdom. Another presentation of the drug product is a cartridge of \_\_\_\_\_ glass and \_\_\_\_\_ rubber. The fill volume of the cartridge is 3 mL. The cartridge formulation contains 5 mg/mL of benzyl alcohol \_\_\_\_\_ in addition to the ingredients described above. The cartridge is to be used with the Becton Dickinson injector-pen (BDPS Pen II) for multi-dose administration, which has been found acceptable by CDRH consult. The sponsor requests \_\_\_\_\_ months expiration dating for both product configurations. Expiration dating of 24 months is justified for the ampule product. Insufficient data are provided to evaluate the stability of the drug product in cartridges.

**B Description of How the Drug Product is Intended to be Used**

The drug product is \_\_\_\_\_ . It is indicated for subcutaneous administration only. The starting dose to treat episodes of immobility is 2 mg. Preparatory and concomitant administration of trimethobenzamide (antiemetic) is recommended because of nausea that can be induced by apomorphine. The dose is titrated in 1 mg increments. Caution is recommended for doses above 6 mg. Instructions are provided to prepare syringes from the ampule and for the manner of injection. Separate instructions are provided for the multiple-use Becton Dickinson delivery pen used with the cartridge. Both the 2 mL ampules and the 3 mL cartridges are provided in cartons of five.

**C Basis for Approvability or Not-Approval Recommendation**

From a CMC perspective, the sponsor has not provided adequate documentation and needs to address the deficiencies listed on pages 53 and 54.

Inspection of the facility provided by DMF \_\_\_\_\_ has not been completed.

### **III Administrative**

#### **A. Reviewer's Signature**

In Division File System

#### **B Endorsement Block**

In Division File System

#### **C CC Block**

Thomas Broadbent CMC Reviewer  
Maryla Guzewska CMC Team Leader  
John Simmons, DNDC1 Division Director  
Hasmukh Patel DNDC1 Deputy Division Director  
Teresa Wheelous Project Manager

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/s/

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CHEMIST

John Simmons  
6/13/03 03 12 53 PM  
CHEMIST  
For M Guzewska