CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209510Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 209510
Assessment 3

Drug Name/Dosage Form	Barhemsys (amisulpride) injection
Strength	2.5 mg/mL, 5 mg amisulpride in 2mL solution, a single-dose vial
Route of Administration	Intravenous use
Rx/OTC Dispensed	Rx
Applicant	Acacia Pharma Ltd., Cambridge, UK
US agent, if applicable	Paul A. Orth, Indianapolis, IN 46250

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SUBMISSION(S) Assessed	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	08/03/2017	OPQ
Resubmission	11/05/2018	OPQ
Resubmission	8/26/2019	OPQ
Amendment	9/24/2019	OPQ
Amendment	9/24/2019	ONDP
Amendment	10/3/2019	OPMA
Labeling	1/15/2020	ONDP
Labeling	1/30/2020	ONDP
Labeling	2/4/2020	ONDP
Labeling	2/14/2020	ONDP
Labeling	2/18/2020	ONDP
Labeling	2/20/2020	ONDP
Labeling	2/21/2020	ONDP
Amendment	2/21/2019	OPMA

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY ASSESSMENT
Drug Substance	Joseph Leginus	Donna Christner
Drug Product and Labeling	Hong Cai	Moo-Jhong Rhee
Process	Laurie Nelson	Vidya Pai
Microbiology	Peggy Kriger	Jesse Wells
Facilities	Laurie Nelson	Vidya Pai
Regulatory Business Process Manager	Oumou Barry	
Application Technical Lead	Hitesh Shroff	
Laboratory (OTR)	N/A	

QUALITY ASSESSMENT

Environmental Analysis (EA)	Hong Cai	Moo-Jhong Rhee

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling issues have been satisfactorily resolved from the CMC perspective.

The Office of Process and Facilities (OPF) has made a final overall "Approval" recommendation for the facilities involved in this application.

This NDA is recommended for **Approval** from the OPQ perspective.

II. Summary of Quality Assessments

This NDA was originally submitted on August 3, 2017 and it was not recommended for approval because of the product quality and facility inspection deficiencies at the drug substance manufacturing facility, (b) (4). A Complete Response (CR) letter was issued on October 5, 2017.

On November 5, 2018 Acacia Pharma submitted an amendment in response to the CR letter. A CR letter was issued on May 2, 2019 because of the product quality and facility inspection deficiencies at the drug substance manufacturing facility, (b) (4) (b) (4).

In response to the CR letter Acacia Pharma submitted an amendment on August 26, 2019. In this amendment Acacia Pharma proposed (b) (4) as a drug substance manufacturer in addition to (b) (4).

In the amendment submitted on February 21, 2020 Acacia Pharma withdrew the second drug substance manufacturer (b) (4). Hence, the drug substance for Barhemsys (amisulpride) injection will be manufactured by only (b) (4) (b) (4).

A. Product Overview

Barhemsys (amisulpride) injection, 5 mg/2 mL is a dopamine D_2 antagonist indicated for prevention of postoperative nausea and vomiting (PONV).

The drug substance, amisulpride, has never been approved as a drug in US, however, it has been approved as tablets and oral solution in Europe for treatment of schizophrenic disorders.

Proposed Indication(s) including Intended Patient Population	Barhemsys (amisulpride) injection is indicated for: • Prevention of postoperative nausea and vomiting (PONV) in adults, either alone or in combination with other antiemetics. (1) • Treatment of (b) (4) PONV in adult patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis. (1)
Duration of Treatment	Administered only once, Maximum 10 mg amisulpride
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:
The drug substance will be manufactured at (b) (4). The drug substance CMC information was reviewed and deemed adequate to support the drug product. An Approval is recommended from the CMC perspective. (**see Drug Substance** Review**)**

Drug Product:
The drug product CMC information was reviewed and deemed adequate. An Approval is recommended from the CMC perspective. (**see Drug Product** Review**)**

Based on satisfactory stability data provided in the application the proposed 60-month expiration dating period when stored at 25ºC/RH 60% is granted.

The Microbiology related sections were reviewed and deemed adequate. An Approval is recommended from the Microbiology perspective. (**see Microbiology** Review**)**

Label/Labeling:
The CMC issues of the labels and labeling were satisfactorily resolved and an approval is recommended from the CMC perspective. (**see Labeling** Review**)**

Facilities and Process:
The drug product manufacturing process at (b) (4) was reviewed and found to be adequate

The Office of Process and Facilities has issued an "Acceptable" recommendation for all manufacturing and testing facilities involved in this application. (see **Manufacturing Integrated Assessment** Review)

C. Lifecycle Management Consideration (NDA only)
None

D. Special Product Quality Labeling Recommendations (NDA only)
None

E. Final Risk Assessment (see Attachment I)

F. List of Deficiencies: None

Attachment I

C. Risk Assessment - NDA 209510

Amisulpride Injection, 5mg/2mL (2.5 mg/mL)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation, Process Parameters	M	(b) (4)		None
pH	API Solubility, particle size	M			None
Bioburden	Manufacturing environment and processes	M			None
Sterility	Sterilization	M			None

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
February 24, 2020

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2020.02.24 10:41:21 -05'00'

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Active	Dr. Joseph Leginus, October 26, 2017,	LOA, May 19, 2017
	Type III			Active	Not reviewed, Information provided in NDA	LOA, July 4, 2016
	Type III			Active	Not reviewed, Information provided in NDA	LOA, December 11, 2015
	Type III			Active	Dr. Denise Miller, March 29, 2019, Adequate	LOA, June 5, 2015

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114207	Amisulpride injection for postoperative nausea and vomiting, Acacia Pharma Ltd., December 21, 2011, active IND

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

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Memorandum

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

Date: **February 21, 2020**

From: **Hong Cai, Ph.D.**
Drug Product Reviewer
Office of New Drug Products
Branch V/DNDP II

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: **CMC Labeling Review #3 of NDA209510**
for BARHEMSYS™ (amisulpride) injection, for intravenous use

Subject: **Final Recommendation - APPROVAL**

On August 26, 2019, the applicant Acacia Pharm Ltd resubmitted the NDA209510 which includes the updated labeling/labels. The applicant has resolved all the CMC related deficiencies of Prescribing Information (PI) including Highlight of Prescribing Information, Section #3, #11 and #16 and Carton and Container Labels (CC labels). Therefore, CMC related information is deemed acceptable from the CMC labeling perspective. The CMC related sections in PI (via email to RPM Mary Chung on February 21, 2020) and CC labels (vial label submitted in SN0056 dated February 4, 2020, single vial carton label submitted in SN0058 dated February 18, 2020 and 10-vial carton label submitted on February 20, 2020, SN0059) are included in this document as the Attachments (Attachment-1 for Prescribing Information and Attachment-2 for the mockup of the container/carton labels).

Recommendation:
This application is recommended for **approval** from the CMC labeling perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

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Hong Cai

Digitally signed by Hong Cai
Date: 2/21/2020 05:16:53PM
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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
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/s/

HITESH N SHROFF
02/24/2020 10:58:17 AM

QUALITY ASSESSMENT

Recommendation: As of this review, this 505 (b)(2) NDA resubmission is *not* ready for Approval in its present form per 21 CFR 314.125(b)(13).

NDA 209510

OPQ Review #2

Drug Name/Dosage Form	Barhemsys (amisulpride) injection
Strength	2.5 mg/mL, 5 mg amisulpride in 2mL solution, a single-dose vial
Route of Administration	Intravenous use
Rx/OTC Dispensed	Rx
Applicant	Acacia Pharma Ltd., Cambridge, UK
US agent, if applicable	Michael Bolinder, Acacia Phrama Inc., Indianapolis, IN

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	08/03/2017	OPQ
Resubmission	11/05/2018	OPQ

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Labeling	Hong Cai	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Li-Shan Hsieh	CDER/OPQ/OPF/ DPAIII/PABVIII
Microbiology	Peggy Kriger	OMPT/CDER/OPQ/OPF/DM A/MABI
Facilities	Laurie Nelson	OMPT/CDER/OPQ/OPF/DIA/IABIII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
Environmental Analysis (EA)	Hong Cai	CDER/OPQ/ONDP/ DNDPII/NDPBV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Active	Dr. Joseph Leginus, October 26, 2017, adequate	LOA, May 19, 2017
	Type III			Active	Not reviewed, Information provided in NDA	LOA, July 4, 2016
	Type III			Active	Not reviewed, Information provided in NDA	LOA, December, 11, 2015

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114207	Amisulpride injection for postoperative nausea and vomiting, Acacia Pharma Ltd., December 21, 2011, active IND

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling is satisfactory from the CMC perspective.

The Office of Process and Facilities (OPF) has ***not*** made a final overall "Approval" recommendation for the facilities involved in this application as of this review.

From the OPQ perspective, this NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(13). **(**see the **List of Deficiencies)**

II. Summary of Quality Assessments

This NDA was originally submitted on August 3, 2017 and it was not recommended for approval because of the product quality and facility inspection deficiencies at the drug substance manufacturing facility, (b) (4). A Complete Response (CR) letter was issued on October 5, 2017.

On November 5, 2018 Acacia Pharma submitted an amendment in response to the CR letter.

A. Product Overview

Amisulpride injection, 5 mg/2 mL is a dopamine D_2 antagonist indicated for prevention of postoperative nausea and vomiting (PONV).

Amisulpride has never been approved as a drug in US, however, it has been approved as tablets and oral solution in Europe for treatment of schizophrenic disorders.

Proposed Indication(s) including Intended Patient Population	Barhemsys (amisulpride) injection is indicated for: • Prevention of postoperative nausea and vomiting (PONV) in adults, either alone or in combination with other antiemetics. (1) • Treatment of (b) (4) PONV in adult patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis. (1)
Duration of Treatment	Administered only once, Maximum 10 mg amisulpride
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:
Approval recommended from the Drug Substance perspective. (**see OPQ Review #1)**

Drug Product:
As stated in the drug product review dated June 1, 2018 a (b) (4) month expiration dating period was granted based on the stability data submitted in the original NDA submission. (**see OPQ Review #1)**

In August 3, 2018 amendment the applicant submitted additional long-term drug product stability data up to 60 months. Based on the long-term and accelerated stability data of the drug product assuring the identity, strength, purity and quality, a 60-month of expiration dating period when stored at 25ºC/RH 60% in the proposed container closure system is granted. (See the **Drug Product** review)

Approval recommended from the Drug Product perspective. (**see Drug Product Review)**

The proposed 60-month expiration dating period when stored at 25ºC/RH 60% is also supported by the microbiology stability data provided in August 3, 2018 amendment. Approval recommended from the Microbiology perspective. (**see Microbiology Review)**

Label/Labeling:
The CMC sections of the labels and labeling were acceptable. (**see Memorandum to OPQ Review #1)**

Facilities and Process:
A follow up pre-approval inspection of the drug substance manufacturing facility, (b) (4) (b) (4) was performed during **March 18 and March 21, 2019**. The OPF Facility reviewer, Dr. Laurie Nelson, concluded the following:

> *"There appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined unacceptable to support approval of this NDA 209510*"

Because of this conclusion, the Office of Process and Facilities has not issued an "Acceptable" recommendation. (see **Facilities Review**)

C. Lifecycle Management Consideration (NDA only)
None

D. Special Product Quality Labeling Recommendations (NDA only)
None

E. Final Risk Assessment (see Attachment I)

F. List of Deficiencies:

Regarding Facilities:
During a recent inspection of the (b) (4) (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility at the close of the inspection. Satisfactory resolution of these observations is required before this NDA may be approved.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
April 24, 2019

ATTACHMENT I: Risk Assessment - NDA 209510

a) Drug Product: Amisulpride Injection, 5mg/2mL (2.5 mg/mL)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation, Process Parameters	M	(b) (4)		None
pH	API Solubility, particle size	M			None
Bioburden	Manufacturing evvironment and processes	M			None
Sterility	Sterilization	M			None

ATTACHMENT II:

List of deficiencies described in the Complete Response Letter sent on October 5, 2018

PRODUCT QUALITY / FACILITY INSPECTIONS

1. During a recent inspection of (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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Hitesh Shroff

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Memorandum

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

Date: **September 28, 2018**
From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 209510**

Subject: Final Recommendation of NOT APPROVAL for NDA 209510

At the time when the CMC Review #1 was completed on June 4, 2018, it had noted the following pending issues:

- The label/labeling issues were not resolved.
- Final "Acceptable" recommendation from the Office of Process and Facilities was not issued.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

On September 17, 2018, the applicant submitted revised labels and labeling. The CMC sections of the labels and labeling were reviewed and found them acceptable (**Attachment - 1)**.

A pre-approval inspection of the drug substance manufacturing facility, (b) (4) was performed between July 16 – July 20, 2018, and the OPF Facility reviewer, Dr. Laurie Nelson, concluded the following:

> *"There appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined unacceptable to support approval of this NDA 209510*" (**Attachment -2**).

Because of this conclusion, the Office of Process and Facilities has not issued an "Acceptable" recommendation.

Recommendation:
From the OPQ perspective, this NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(13).

Application Technical Lead's Assessment and Signature

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
September 28, 2018

Memorandum

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

Date: **September 17, 2018**

From: **Hong Cai, Ph.D.**
Drug Product Reviewer
Office of New Drug Products
Branch V/DNDP II

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: **CMC Labeling Review #1 of NDA209510**
for BARHEMSYS™ (amisulpride) injection, for intravenous use

Subject: **Final Recommendation - APPROVAL**

At the time when Labeling Review of NDA209510 was completed on May 29, 2018, this NDA was not recommended for approval in its original form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (Prescribing Information, container/carton) negotiations had not been completed, and in its original form, the labeling did not comply with the requirements under 21 CFR 201. The NDA for this drug product was otherwise complete and adequate from the drug product perspective.
Per FDA Liaison to USAN Council, Dr. David Lewis via email on September 13, 2018, the proposed established name for API, amisulpride, is scheduled to be formally adopted as a USAN name on September 26, 2018." (see Attachment-1).

On September 17, 2018, the applicant Acacia Pharm Ltd provided the most updated Prescribing Information and Carton and Container Label/Labeling (SN0038) based on FDA proposed edits. Attachment-2 is the CMC related sections of Prescribing Information and Attachment-3 contains the mockup of the container/carton labels. For the vial label, the storage condition has been revised per the Agency's recommendation (Attachment -4) to include the following statement, *"Protect from light.* (b) (4) (b) (4). The revised labels and Prescribing Information are deemed acceptable from the CMC labeling perspective.

Recommendation:
The previously noted outstanding CMC label/labeling issues have been satisfactorily resolved, and therefore, this application is now recommended for **approval** from the labeling perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Attachment-1:

From: Shroff, Hitesh
To: Hong Cai; Leginus, Joseph
Cc: Shroff, Hitesh
Subject: FW: NDA 209510 - Amisulpride injection - REQUEST
Date: Thursday, September 13, 2018 12:58:39 PM

Hi Hong Cai and Joe

Please see email below from David. Amisulpride is adopted as USAN name.

Thanks.

Hitesh Shroff
CMC Lead
CDER/OPQ/ONDP
Bldg: 21 Rm: 1667
☎: 6-2116

From: Lewis, David B
Sent: Thursday, September 13, 2018 11:03 AM
To: Shroff, Hitesh <Hitesh.Shroff@fda.hhs.gov>
Cc: Christner, Donna <Donna.Christner@fda.hhs.gov>
Subject: RE: NDA 209510 - Amisulpride injection - REQUEST

The name *amisulpride* was submitted in USAN ballot FG-201. All votes have been collected. The name is already a recommended INN. All votes concerning the USAN ballot were confirmatory. The name *amisulpride* is scheduled to be formally adopted as a USAN name on September 26th, 2018 (according to the USAN Council director).

David Lewis
FDA liaison to the USAN Council

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Attachment-4

From: Abraham, Sherly
Sent: Friday, August 24, 2018 11:05 AM
To: Cai, Hong <Hong.Cai@fda.hhs.gov>; Vee, Sarah <Sarah.Vee@fda.hhs.gov>
Subject: RE: NDA 209510 Barhemsys Storage Condition on Vial Label

Looks good to me.

Sherly Abraham, RPh
Safety Evaluator

Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
U.S. Food and Drug Administration
Tel: (301) 796 3198
sherly.abraham@fda.hhs.gov

From: Cai, Hong
Sent: Friday, August 24, 2018 11:03 AM
To: Abraham, Sherly <Sherly.Abraham@fda.hhs.gov>; Vee, Sarah <Sarah.Vee@fda.hhs.gov>
Subject: RE: NDA 209510 Barhemsys Storage Condition on Vial Label

Hi Sherly,
Thanks for the quickly response.
Please see my comment to the applicant and feel free to revise if needed. Thanks.
Hong

1. *The storage condition statement on the container and carton label/labeling should be consistent with section #16 How Supplied/Storage and Handling of the product Prescribing Information. Revise the 10-vial carton labeling storage statement* (b) (4) (b) (4) *to "Administer BARHEMSYS within 12 hours after the vial is removed from the protective carton."*

   For the vial label, make the storage condition (the temperature) smaller and put "protect from light. (b) (4)*" if there is a space limitation.*

Hong Cai

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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
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Hitesh Shroff

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QUALITY ASSESSMENT

Recommendation: As of this review, this 505 (b)(1) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(13) and 21 CFR 314.125(b)(6).

NDA 209510

OPQ Review #1

Drug Name/Dosage Form	Barhemsys (amisulpride) injection
Strength	2.5 mg/mL, 5 mg amisulpride in 2mL solution, a single-dose vial
Route of Administration	Intravenous use
Rx/OTC Dispensed	Rx
Applicant	Acacia Pharma Ltd., Cambridge, UK
US agent, if applicable	Michael Bolinder, Acacia Phrama Inc., Indianapolis, IN

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	8/3/2017	OPQ
Amendment	11/13/2017	OPF/DIA/IABIII and OPF/DMA/MABI
Amendment	11/24/2017	ONDP
Amendment	1/11/2018	ONDP and OPF/DIA/IABIII
Amendment	3/13/2018	OPF/DMA/MABI, ONDP and OPF/DIA/IABIII
Amendment	4/13/2018	ONDP
Amendment	4/18/2018	ONDP and OPF/DMA/MABI
Amendment	4/30/2018	ONDP and OPF/DMA/MABI
Amendment	5/23/2018	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Labeling	Hong Cai	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Li-Shan Hsieh	CDER/OPQ/OPF/ DPAIII/PABVIII
Microbiology	Peggy Kriger	OMPT/CDER/OPQ/OPF/DM A/MABI
Facilities	Laurie Nelson	OMPT/CDER/OPQ/OPF/DIA/IABIII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
Environmental Analysis (EA)	Hong Cai	CDER/OPQ/ONDP/ DNDPII/NDPBV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Active	Dr. Joseph Leginus, October 26, 2017, adequate	LOA, May 19, 2017
	Type III			Active	Not reviewed, Information provided in NDA	LOA, July 4, 2016
	Type III			Active	Not reviewed, Information provided in NDA	LOA, December, 11, 2015

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114207	Amisulpride injection for postoperative nausea and vomiting, Acacia Pharma Ltd., December 21, 2011, active IND

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities (OPF) has ***not*** made a final overall "Approval" recommendation for the facilities involved in this application as of this review.

The label/labeling issues have ***not*** been satisfactorily resolved.

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per 21 CFR 314.125(b)(13) and 21 CFR 314.125(b)(6) , until above mentioned issues are satisfactorily resolved. **(**see the **List of Deficiencies)**

II. Summary of Quality Assessments

A. Product Overview

Amisulpride injection, 5 mg/2 mL is a dopamine D_2 antagonist indicated for prevention of postoperative nausea and vomiting (PONV).

Amisulpride has never been approved as a drug in US, however, it has been approved as tablets and oral solution in Europe for treatment of schizophrenic disorders.

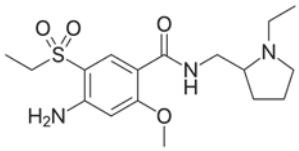
Proposed Indication(s) including Intended Patient Population	Barhemsys (amisulpride) injection is indicated for: • Prevention of postoperative nausea and vomiting (PONV) in adults, either alone or in combination with other antiemetics. (1) • Treatment of (b) (4) PONV in adult patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis. (1)
Duration of Treatment	Administered only once, Maximum 10 mg amisulpride
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:
The active ingredient, Amisulpride, is a white to almost white crystalline powder. It is practically insoluble in water. Amisulpride is a chiral compound. It is produced as a racemic mixture of equal amount of R and S enantiomers and shows no optical rotation. It is not hydrophobic and no other amisulpride polymorphs are known.

Amisulpride is manufactured by (b) (4). The complete CMC information is provided in DMF (b) (4) from the manufacturer. A letter of authorization from the manufacturer dated March 31, 2017 was provided. This DMF was reviewed by Dr. Joseph Leginus on October 26, 2017 and was deemed adequate.

Its chemical 4-amino-*N*-[[(2*RS*)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl) -2-methoxybenzamide. It has the following chemical structure:



The empirical formula is $C_{17}H_{27}N_3O_4S$, with a molecular weight of 369.48. Its melting point is (b) (4) to 126°C.

The applicant has provided Certificate of Analysis (COA) of all nine batches of the drug substance used in the manufacture of the drug product including the batch used to manufacture the clinical drug product batch.

The identity, purity and quality of the drug substance, amisulpride, is controlled by its specification which includes appearance, identification by infrared spectroscopy, assay by potentiometric titration, impurities by HPLC, and bioburden and sterility tests. In addition, the drug substance specification also includes controls for particle size distribution (b) (4). The drug substance specification is deemed adequate per drug substance reviewer, Dr. Joseph Leginus. (See **the Drug Substance** review)

Based on the long-term and accelerated stability data of three registration batches of amisulpride provided in DMF (b) (4), a re-test period of (b) (4) months at (b) (4) was established when stored (b) (4) (b) (4).

The Office of Process and Facilities (OPF) reviewer, Dr. Laurie Nelson has *not* made an "Adequate" recommendation for all drug substance manufacturing and testing facilities. (See the **Facilities** review)

The API are manufactured by (b) (4) is controlled to conform to the requirements (specification) to produce Amisulpride injection, 5 mg/ 2mL.

Drug Product:
Amisulpride injection is a clear, colorless, nonpyrogenic, sterile solution containing amisulpride in a single-dose glass vial. Each 2-mL vial of amisulpride injection contains 5 mg of amisulpride; 18.7 mg of citric acid monohydrate; 3.6 mg of sodium chloride; 32.64 mg of trisodium citrate dihydrate; (b) (4) hydrochloric acid and sodium hydroxide as required to adjust the pH; and Water for Injection USP to make up to volume. The drug product does not contain any preservatives or antioxidants. A single 5 mg or 10 mg dose is infused intravenously over 1 to 2 minutes at the time of induction of anesthesia.

The drug product is manufactured by (b) (4). The manufacturing process consists (b) (4) (b) (4) The process selection, in-process controls, drug product release tests and executed batch records were satisfactory. The drug product manufacturing process was reviewed by Dr. Li-Shan Hsieh and was deemed acceptable. (See **Process** review)

The overall control strategy for the drug product's identity, strength, purity and quality deemed adequate based on raw material controls, drug product specification including appearance, identity, assay, impurities, extractable volume, particulate matter, pH, osmolality, bacterial endotoxin limits, and sterility. For assay and impurities determinations, the applicant developed and used non-compendial, validated in-house methods.

Based on the long-term and accelerated stability data of the drug product assuring the identity, strength, purity and quality, a (b) (4) month of expiration dating period when stored at refrigerated temperature (5ºC ±3ºC) in the proposed container closure system is granted. (See the **Drug Product** review)

The environmental monitoring at (b) (4) manufacturing process (b) (4) (b) (4) (b) (4) as well as the microbiology related attributes in the drug product specification including endotoxins, sterility and container closure integrity etc. were reviewed by Dr. Peggy Kriger and recommended this NDA for approval based on drug product sterility assurance. (See the **Microbiology** review)

The Office of Process and Facilities (OPF) reviewer, Dr. Laurie Nelson, has made an "Adequate" recommendation for the drug product manufacturing and testing facilities. (See the **List of Deficiencies** below and the **Facility** review)

The applicant requested categorical exclusion for environmental analysis on the basis that the concentration of amisulpride at the point of entry into aquatic environment is estimated to be less than (b) (4) ppb and no extraordinary circumstances exist. Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 was deemed acceptable. (See

the **Drug Product** review of Dr. Hong Cai)

The labels and labeling issues are ***not*** satisfactorily resolved from the CMC perspective per the labeling reviewer, Dr. Hong Cai. (See the **List of Deficiencies** below and **Labeling** review).

C. Lifecycle Management Consideration (NDA only)
None

D. Special Product Quality Labeling Recommendations (NDA only)
None

E. Final Risk Assessment (see Attachment)

F. List of Deficiencies:

A. Regarding Facilities:
The Office of Process and Facilities (OPF) has not made an "Adequate" recommendation for all drug substance manufacturing and testing facilities.

B. Regarding labeling:
The following labeling comments should be resolved with the applicant.

Prescription Information:

1. Replace (b) (4) with accepted trade name throughout the entire PI document.
2. In the "Description" section (#11): Include the presentation of the proprietary name and established name. Suggested revision:
   a) From (b) (4) (b) (4) To "Tradename (amisulpride) injection is a clear, colorless, nonpyrogenic, sterile solution formulation of amisulpride 5 mg/2 mL (2.5 mg/mL) for intravenous infusion presented in a single-dose vial."
   b) Revise the pharmacological class/therapeutic class description to "a selective dopamine-2 (D2)".
   c) The drug substance is racemate. Update the structure accordingly.
   d) The inactive statement should be consistent with the drug product composition stated in NDA. Also, add the pH range of the formulation (pH4.75-5.25) in the inactive components section.
3. In the "How supplied/storage and Handling "section (#16): The storage condition should be revised to be specific for the vials removed from the protection cartoon. Revise (b) (4) (b) (4) To "Administration of drug product should occur within 12 hours after the vial is removed from the protective carton."

Labels:

For the vial label:

1. Provide the manufacturer/distributor name as required by 21 CFR 201.10(i).
2. Provide the bar code, unless "FPO" is for bar code place holder.

For the 10-vial package label:

1. Add the "Rx only" statement

For All Labels:

1. Revise the term [redacted] (b) (4) to "single-dose vial".
2. The storage condition statement should be consistent with PI.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
June 04, 2018

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2018.06.04 15:56:11 -04'00'

LABELING

IQA Review Guide Reference

I. Package Insert

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4).

(b) (4) (amisulpride) injection, for intravenous use

Initial U.S. Approval: [YYYY] (b) (4)

---------- INDICATIONS AND USAGE ----------

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	(b) (4) ® (amisulpride) injection	**Satisfactory** The presentation is correct. However, replace the tradename (b) (4) with accepted name throughout the document.
Dosage form, route of administration	Injection, for intravenous use	**Satisfactory**
Controlled drug substance symbol (if applicable)	N/A	**N/A**

Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	Injection (b) (4) (b) (4): 5 mg/2 mL (2.5 mg/mL) in a single-dose vial. (3)	**Satisfactory**

2. ***Section 2 Dosage and Administration***

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended adult dosage of BARHEMSYS by indication is shown in the table below:

Indication	Adult Dosage Regimen
Prevention of PONV	5 mg as a single intravenous injection infused over 1 to 2 minutes at the time of induction of anesthesia *[see Dosage and Administration (2.2)]*.
Treatment of PONV	10 mg as a single intravenous injection infused over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure *[see Dosage and Administration (2.2)]*.

2.2 Preparation and Administration

Dilution of BARHEMSYS is not required before administration. BARHEMSYS is chemically and physically compatible with Water for Injection, 5% Dextrose Injection and 0.9% Sodium Chloride Injection, which may be used to flush an intravenous line before or after administration of BARHEMSYS.

BARHEMSYS is subject to photodegradation (b) (4). (b) (4) within 12 hours of removal of the vial (b) (4) (b) (4) from the protective carton.

(b) (4) administration, inspect the BARHEMSYS solution for particulate matter and discoloration; (b) (4).

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	See the information pasted above which is from the amendment submitted on April 23, 2018 in SN0023.	**Satisfactory** The assessment is based on the applicant revised proposed on April 23, 2018. Only Section 2.2 has been reviewed from drug product perspective.

3. ***Section 3 Dosage Forms and Strengths***

3 DOSAGE FORMS AND STRENGTHS

Injection (b) (4): 5 mg/2 mL (2.5 mg/mL) as a clear, colorless, (b) (4) sterile solution in a single-dose vial.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	Injection (b) (4) (b) (4):	**Satisfactory**
Strengths: in metric system	5 mg/2 mL (2.5 mg/mL)	**Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	NA	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	as a clear, colorless, (b) (4) sterile solution in a single-dose vial	**Satisfactory**

4. ***Section 11 Description***

11 DESCRIPTION

The active ingredient of (b) (4) is amisulpride, a (b) (4) receptor antagonist. Its chemical name is (b) (4). It has the following chemical structure:

(b) (4)

The empirical formula is $C_{17}H_{27}N_3O_4S$ representing a molecular weight of 369.48.

Amisulpride is a white or almost white crystalline powder. It is practically insoluble in water, sparingly soluble in ethanol and freely soluble in methylene chloride, and has a melting point of around 126°C. The compound is racemic and shows no optical rotation and is not hygroscopic. No other polymorphs of amisulpride have been reported.

(b) (4) is a clear, colorless, nonpyrogenic, sterile solution (b) (4) formulation of amisulpride 5 mg/2 mL (2.5 mg/mL) for intravenous (b) (4) presented in a single-dose vial. It has a pH of approximately 5.0 and the osmolality of the product is between 250 and 330 mOsmol/kg.

Each 2 mL vial of (b) (4) contains 5 mg of amisulpride; 18.7 mg of citric acid monohydrate USP; 3.6 mg of sodium chloride USP; 32.64 mg of trisodium citrate dihydrate USP; (b) (4) hydrochloric acid NF and sodium hydroxide NF as (b) (4) to adjust the pH; and Water for Injection USP to make up to volume.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	(b) (4) is a clear, colorless, nonpyrogenic, sterile solution (b) (4) formulation of amisulpride 5 mg/2 mL (2.5 mg/mL) for intravenous (b) (4) presented in a single-dose vial.	**Not Satisfactory** The presentation of the proprietary name and the established name is not correct. Revise to "Tradename (amisulpride) Injection is a clear, colorless, nonpyrogenic, sterile solution formulation of amisulpride 5 mg/2 mL (2.5 mg/mL) for intravenous infusion presented in a single-dose vial."
Dosage form and route of administration	(b) (4) is a clear, colorless, nonpyrogenic, sterile solution (b) (4) formulation of amisulpride 5 mg/2 mL (2.5 mg/mL) for intravenous (b) (4) presented in a single-dose vial.	**Not Satisfactory** See the revision above in the Proprietary name and established name section.
Active moiety expression of strength with equivalence statement (if applicable)	NA	NA

For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each 2 mL vial of (b) (4) contains 5 mg of amisulpride; 18.7 mg of citric acid monohydrate USP; 3.6 mg of sodium chloride USP; 32.64 mg of trisodium citrate dihydrate USP; (b) (4) hydrochloric acid NF and sodium hydroxide NF as required to adjust the pH; and Water for Injection USP to make up to volume.	**Not Satisfactory** Revise "adjust the pH" to "adjust pH (4.75-5.25)"
Statement of being sterile (if applicable)	(b) (4) is a clear, colorless, nonpyrogenic, sterile solution injection formulation of amisulpride 5 mg/2 mL (2.5 mg/mL) for intravenous administration presented in a single-dose vial.	**Satisfactory**
Pharmacological/ therapeutic class	a (b) (4) receptor antagonist	**Not Satisfactory** Revise to "a (b) (4) dopamine-2 (D_2)" per clinical team.
Chemical name, structural formula, molecular weight	Its chemical name is 4 amino-N-[[(2RS)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide. It has the following chemical structure: (b) (4) The empirical formula is $C_{17}H_{27}N_3O_4S$ representing a molecular weight of 369.48.	**Not Satisfactory** The drug substance is racemate. Update the structure accordingly.
If radioactive, statement of important nuclear characteristics.	NA	NA

Other important chemical or physical properties (such as pKa or pH)	Amisulpride is a white or almost white crystalline powder. It is practically insoluble in water, sparingly soluble in ethanol and freely soluble in methylene chloride, and has a melting point of around 126°C. The compound is racemic and shows no optical rotation and is not hygroscopic. No other polymorphs of amisulpride have been reported.	**Satisfactory**

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) Injection is supplied as follows:

NDC 71390-125-20: Package of 10 cartons. Each carton (NDC 71390-125-21) contains one clear, colorless, single-dose vial of (b) (4) Injection, 5 mg in 2 mL (2.5 mg/mL).

Store vials at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

Protect from light. (b) (4)

17 PATIENT COUNSELING INFORMATION

QT Prolongation

Instruct patients to contact their health care provider immediately if they perceive a change in their heart rate, if they feel lightheaded, or if they have a syncopal episode *[see Warnings and Precautions (5.1)]*.

Drug Interactions

Advise patients to report to their healthcare provider if they are taking (b) (4) (b) (4) drugs which prolong the QT interval *[see Warnings and Precautions (5.1)]*.

Distributed by Acacia Pharma Inc, Indianapolis, IN, USA.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	Each carton (NDC 71390-125-21) contains one clear, colorless, single-dose vial of (b) (4) Injection, 5 mg in 2 mL (2.5 mg/mL).	**Satisfactory**
Available units (e.g., bottles of 100 tablets)	NDC 71390-125-20: Package of 10 cartons. Each carton (NDC 71390-125-21) contains one clear, colorless, single-dose vial of (b) (4) Injection, 5 mg in 2 mL (2.5 mg/mL).	**Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 71390-125-20: Package of 10 cartons. Each carton (NDC 71390-125-21) contains one clear, colorless, single-dose vial of (b) (4) Injection, 5 mg in 2 mL (2.5 mg/mL).	**Satisfactory**
Special handling (e.g., protect from light)	Protect from light. (b) (4) (b) (4)	**Not Satisfactory** Revise to: "(b) (4) (b) (4) within 12 hours after the vial is removed from the protective carton."
Storage conditions	Store vials at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from light. (b) (4) (b) (4)	**Not Satisfactory** Revise to: "(b) (4) (b) (4) within 12 hours after the vial is removed from the protective carton."
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Distributed by Acacia Pharma Inc, Indianapolis, IN, USA. © (b) (4), Acacia Pharma. All rights reserved.	**Satisfactory**

Reviewer's Assessment of Package Insert: ***Inadequate***

Review comments are made on the Prescribing Information which is based on the submission dated January 30, 2018 (SN0014) and updated amendment for section 2.2 submitted on April 23, 2018 (SN0023).

As of this review, the Prescribing Information is not deemed satisfactory from the CMC labeling perspective (See "**List of the deficiencies**" at the end of this review).

II. Labels:

1. ***Container (vial) Label***

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4) (amisulpride) injection	**Satisfactory** Note: Tradename is not approved yet by FDA at this time.
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	5 mg|2mL (2.5 mg/mL)	**Satisfactory**
Net quantity of dosage form	5 mg/2 ml (2.5 mg/mL) 2-mL (b) (4) sterile vial	**Not Satisfactory** Revise (b) (4) to "single-dose".
"Rx only" displayed prominently on the main panel	Rx only	**Satisfactory**
Lot number and expiration date	LOT: EXP:	**Satisfactory**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Not provided	**Satisfactory** It is acceptable for not provide the storage condition due to the space limitation with the vial label.
Bar code (21CFR 201.25)	Not provided	**Not Satisfactory** Provide the bar code unless the FPO is for bar code.
NDC number (21 CFR 207.35(b)(3)(i))	NDC 71390-125-21	**Satisfactory**
Manufacturer/distributor's name	Not provided	**Not Satisfactory** Provide the manufacturer information
Quantitative ingredient information (injectables)	Not provided	**Satisfactory** It is acceptable due to the space limitation. This information is provided in vial carton and 10-vial carton box.
Statement of being sterile (if applicable)	2-mL (b) (4) sterile vial	**Satisfactory** Term (b) (4) should be revised to "single-dose".

2. Carton Label

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4)™ (amisulpride) injection	**Satisfactory**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	5 mg|2mL (2.5 mg/mL)	**Satisfactory**
Net quantity of dosage form	5mg/2mL Each 2-mL vial contains 5 mg amisulpride	**Satisfactory**
"Rx only" displayed prominently on the main panel	Rx only	**Satisfactory**
Lot number and expiration date	LOT: EXP:	**Satisfactory**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Storage: 20°C – 25°C (68°F – 77°F), see USP for Controlled Room Temperature. Protect vial from light. (b) (4) (b) (4)	**Not Satisfactory** Revise (b) (4) (b) (4) (b) (4) to (b) (4) within 12 hours after the vial is removed from the protective carton."
Bar code (21CFR 201.25)	Provided the place holder	**Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	NDC 71390-125-21	**Satisfactory**
Manufacturer/distributor's name	Manufactured for: Acacia Pharma, Inc., Indianapolis, IN 46240 USA	**Satisfactory**
Quantitative ingredient information (injectables)	Each 2-mL vial contains 5 mg amisulpride, 18.7 mg citric acid monohydrate, 32.6 mg trisodium citrate dihydrate, 3.6 mg sodium chloride and water for injection. (b) (4) (b) (4)	**Satisfactory**

Statement of being sterile (if applicable)	(b) (4) sterile vial	**Satisfactory** However, revise the term (b) (4) to "single-dose".

10 Vial Package Label Only

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4)™ (amisulpride) injection For Intravenous Use Only	**Satisfactory**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	5 mg|2mL (2.5 mg/mL)	**Satisfactory**
Net quantity of dosage form	Each 2-mL vial contains 5 mg amisulpride	**Satisfactory**
"Rx only" displayed prominently on the main panel	Not Provided with 10 vial package label.	**Not Satisfactory** Include the statement of "Rx only".
Lot number and expiration date	Lot: Exp:	**Satisfactory**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Storage: 20°C – 25°C (68°F – 77°F), see USP for Controlled Room Temperature. Protect vial from light. (b) (4) (b) (4)	**Not Satisfactory** Revise (b) (4) (b) (4) (b) (4) to (b) (4) within 12 hours after the vial is removed from the protective carton."
Bar code (21CFR 201.25)	Provided the place holder	**Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	10 vial package label: NDC 71390-125-20	**Satisfactory**
Manufacturer/distributor's name	Manufactured for: Acacia Pharma, Inc., Indianapolis, IN 46240 USA	**Satisfactory**
Quantitative ingredient information (injectables)	Each 2-mL vial contains 5 mg amisulpride, 18.7 mg citric acid monohydrate, 32.6 mg trisodium citrate dihydrate, 3.6 mg sodium chloride and water for injection. (b) (4)	**Satisfactory**
Statement of being sterile (if applicable)	Sterile. Non-pyrogenic aqueous solution that is clear and colorless.	**Satisfactory**

Reviewer's Assessment of Labels: ***Inadequate from CMC perspective***

The above review comments for the container and closure labels are based on the original submission of NDA209510 on August 3, 2017 (SN0001), and as of this review, the labels for container and cartons are not deemed satisfactory from the CMC perspective (see the following **List of deficiencies**).

List of Deficiencies:

A. Regarding Prescription Information:

1. *Replace* (b) (4) *with accepted trade name throughout the entire PI document.*

2. *In the "Description" section (#11): Include the presentation of the proprietary name and established name. Suggested revision:*

   a) ***From*** (b) (4) (b) (4)

   To *"Tradename (amisulpride) injection is a clear, colorless, nonpyrogenic, sterile solution formulation of amisulpride 5 mg/2 mL (2.5 mg/mL) for intravenous infusion presented in a single-dose vial."*

   b) *Revise the pharmacological class/therapeutic class description to "a selective dopamine-2 (D2)".*

   c) *The drug substance is racemate. Update the structure accordingly.*

   d) *The inactive statement should be consistent with the drug product composition stated in NDA. Also, add the pH range of the formulation (pH4.75-5.25) in the inactive components section.*

3. *In the "How supplied/storage and Handling "section (#16): The storage condition should be revised to be specific for the vials removed from the protection cartoon. Revise* (b) (4) (b) (4) *To "Administration of drug product should occur within 12 hours after the vial is removed from the protective carton."*

B. Regarding Labels

For the vial label:

1. *Provide the manufacturer/distributor name as required by 21 CFR 201.10 (i).*
2. *Provide the bar code, unless "FPO" is for bar code place holder.*

For the 10 vial package label:

1. *Add the "Rx only" statement*

For All Labels:

1. *Revise the term* [redacted] (b) (4) *to "single-dose vial".*
2. *The storage condition statement should be consistent with PI.*

Overall Assessment and Recommendation:

From the ONDP perspective, this application is ***not*** deemed ready for approval in its present form per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Drug product Reviewer
Branch V/DNDP II/ONDP/OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Cai's assessment on the labeling and labels, and concur with her recommendation that this NDA is not ready for approval as of this review.

Moo-Jhong Rhee, Ph.D.
Chief
Branch V/DNDP II/ONDP/OPQ

Hong Cai

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Moo Jhong Rhee

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Date: 5/30/2018 12:36:38PM
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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background: 505(b)(2)

NDA: 209510

Drug Product Name/Strength: Amisulpride Injection/2.5 mg/mL in a 2 mL/13 mm vial, single dose

Route of Administration: Intravenous Injection

Applicant Name: Acacia Pharma Ltd.

Manufacturing Site: (b) (4)

(b) (4)

Method of Sterilization: (b) (4)

***Review Recommendation*: Adequate**

***Review Summary*:** (b) (4)

(b) (4)

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
8/3/17	8/3/17	N/A	10/23/17
11/10/17	11/13/17	N/A	N/A
1/11/18	1/11/18	N/A	N/A
3/13/18	3/13/18	N/A	N/A
4/3/18	4/3/18	N/A	N/A
4/18/18	4/18/18	N/A	N/A
4/23/18	4/23/18	N/A	N/A
4/30/18	4/30/18	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The submission is in the eCTD format. The 11/10/17 amendment is referenced in response to an IR sent on 11/8/17. The 1/11/18 amendment is referenced for stability data. The 3/13/18 and 4/18/18 amendments are referenced for responses to the 2/27/18 CMC information request letter. The 4/3/18 amendment is referenced for the response to the 3/20/18 CMC information request letter. The 4/23/18 and 4/30/18 amendments are referenced for the response to the 4/12/18 CMC information request letter. Some tables were copied from the submission.

Concise Description Outstanding Issues Remaining: None identified

Supporting Documents:
DMF (b) (4) is referenced for (b) (4). An LOA (dated April 3, 2017) is provided. Relevant information was reviewed in the document 18370mic14.docx (dated May 8, 2018, adequate).

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Clear, colorless, sterile solution
- **Drug product composition** –

Ingredient	Content per vial (mg per 2 mL dose)	Function
Amisulpride	5	Active ingredient
Trisodium citrate dihydrate	32.64	Excipient
Citric acid monohydrate	18.7	Excipient
Sodium chloride	3.6	Excipient
Hydrochloric acid	q.s.	pH adjusting agent
Sodium hydroxide	q.s.	pH adjusting agent
Water for Injection	(b) (4)	

- **Description of container closure system** –

Configuration	Component	Description	Manufacturer
5 mg/vial as 2.5 mg/mL	Vial	(b) (4)	
	Stopper		
	Seal		

Reviewer's Assessment: Adequate

The description of the drug product and container closure system is satisfactory.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(11/10/17 amendment "cover-0006.pdf", "container-closure-system.pdf", p.33; 3/13/18 "cover-0019.pdf"; 4/30/18 "cover-0024.pdf")

Test method: Dye ingress
Brief description: See below under 4/30/18 amendment response
Positive controls:

- Reference – (b) (4) 0.1% Methylene blue dye is added to a product vial
- Breached – not used

Negative/blank: Finished product vial that is not immersed in dye
Limit of Detection (LOD): (b) (4) of 0.1% dye solution
Acceptance criteria:

- No vial has a different color from the "Blank vial".

- If there is a non-conforming vial, check that the vial is intact and free from cracks or breaking points in the glass. In this case, it is possible to exclude this sample from the evaluation.

(b) (4) 100% testing is performed with visual checks and an automated method.

Reviewer's Assessment: Adequate

Note to reviewer: The CCIT study summary was submitted in response to an Information Request at the time of filing. Clarification was requested as relevant study information was not provided. In addition, as the preferred detection method for dye ingress is by spectrophotometer, not only visual, information regarding method robustness was requested of the sponsor.

The following deficiency was issued in the 2/27/18 information request:

Deficiency: The summary for validation of container closure integrity testing submitted in the 11/10/17 amendment is acknowledged. However, the information is incomplete. Please address the following:

a) It is acknowledged that the container closure system used for validation is the same as proposed for the subject drug product; however, whether the test samples used for the study were exposed to the maximum commercial production conditions before the integrity testing is unclear. Indicate the type of test samples used and whether the vials used for testing were processed by the proposed manufacturing process, including (b) (4)

Applicant's response (3/13/18 amendment): The samples (Batch 0001) were manufactured by the proposed manufacturing process, but collected (b) (4) (b) (4) The method will be revalidated with vials that were (b) (4).

b) Provide the validation study date, number of test samples, number of positive and negative controls and results of the testing.

Applicant's response (3/13/18 amendment): The validation study was performed on June 29, 2016. One positive and one negative control was used. The number of test samples was 314 vials. Results – no test vial had a different color from the negative control when compared visually.

c) Describe whether breached positive controls were used in testing, and if not, provide a justification.

Applicant's response (3/13/18 amendment): The applicant describes the 'breached' control as one drug product sample vial to which (b) (4) 0.1% dye has been added.

d) It is noted that the method is based on visual, as opposed to spectrophotometric, detection. Demonstrate that the current visual method is capable of producing reliable and reproducible results.

Applicant's response (3/13/18 amendment): The applicant states that the method is a verified standard test and considers the method to be reliable and reproducible. A study

was performed on Feb. 17, 2015 with vials of the subject drug product, from engineering batch TT288, in which 250 vials with (b) (4) and 250 vials with (b) (4) were tested. Results - no vials were different from the control vial in color.

Note to reviewer: As the 2016 validation study of container closure integrity testing was performed on samples not subjected to (b) (4) a new CCIT summary was requested. In addition, clarification was again requested about the use of a breached control and testing related to validation of container closure integrity if (b) (4) (b) (4) will be performed.

The following deficiency was issued in the 4/12/18 information request:

Deficiency: Regarding container closure integrity testing, the information request response in "cover-0019.pdf" is acknowledged. However, please address the following:

a) As the test samples used in the container closure integrity testing were not exposed to (b) (4), provide a summary of the validation testing with samples that are representative of the full manufacturing process, including (b) (4). Include at a minimum - validation study date, method, description and size of vials and container closures, number of test samples, number of positive and negative controls, and results of testing.

Applicant's response (4/30/18 amendment): Qualification Report AS094RQM06 Vers.No.01, dated April 24, 2018, is provided and reviewed below.

The container/closure used for integrity testing is the same as used for the subject drug product – (b) (4) vial, from the subject drug product (APD-421) batch 00001, subjected to the full manufacturing process, including (b) (4).

Test method: Dye ingress

(b) (4)

Test samples: Ten subject drug product vials (2.5 mg/mL) per run

Breached positive controls: (b) (4)

(b) (4)

Negative/blank: Finished product vial that is not immersed in dye

Acceptance criteria:

- Positive controls: Visible presence of Methylene Blue solution in all vials
- Test samples: None of the vials with visible leaks of Methylene Blue solution

Results: A summary table and pictures are provided for the results.

Sample	# Positive/ # Tested		
	Run 1	Run 2	Run 3
Test unit	0/10	0/10	0/10
Breached control	2/2	2/2	2/2

The acceptance criteria were met.

b) If the subject drug product may be exposed to multiple (b) (4) cycles (b) (4) (b) (4), describe how the container closure integrity of the samples after maximum processing has been tested.

Applicant's response (4/30/18 amendment): There is no (b) (4) proposed for the manufacturing process. The container closure system will not be exposed to multiple (b) (4) cycles.

c) It is acknowledged that the positive control is prepared by adding (b) (4) 0.1% dye to a product vial and that (b) (4) of dye is the limit of detection. However, it is still unclear if a breached control has been used during testing. (b) (4) (b) (4) (b) (4). A breached vial is a typical positive control for CCIT. Indicate if a breached vial has been used during validation testing and, if not, provide a justification.

Applicant's response (4/30/18 amendment): Breached positive controls were used in the requalification of the container closure integrity test. Five batches of the subject drug product were also tested with the revised method, using a breached positive control and a negative control. The container closures were the same as the commercial product, and tested after (b) (4) Analytical Report AS094PVR05 Vers.No.02, dated April 30, 2018, is provided. The results are noted in the table below:

Sample batch	Acceptance criteria	# Positive/ # Tested
TT288	No sign of leakage should be visible	0/30
00001		0/30
00002		0/30
00003		0/30
00004		0/30

The acceptance criteria were met.

Antimicrobial Effectiveness Testing

Reviewer's Assessment: N/A

The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

Drug product manufacturing, release and stability testing:

(b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

A brief description of the manufacturing building and facilities is provided.

Overall Manufacturing Operation

(b) (4)

14 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

P.7 Container Closure - See P.1

P.8 Stability

P.8.1 Stability Summary and Conclusion

Proposed Expiry: 36 months

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial endotoxins	USP <85>	< (b) (4) EU/mL
Sterility	USP <71>	No growth of microorganisms

Stability storage conditions: 30°C/65% RH*, inverted orientation

Test	Time (Months)					
	0	12	24	36	48	60
Bacterial endotoxins	X	X	X	X	X	X
Sterility	X	X	X	X	X	X

*Samples stored at 25°C/60% RH will be tested if failures are observed in other conditions.

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer's Assessment: Adequate

P.8.3 Stability Data

For exhibit batch #(s) 00001 and 00002, results for bacterial endotoxins and sterility testing complied with the drug product stability specification at the twelve-month time point.

Earlier pilot batch #(s) PD13068 and PD13069, and clinical batch # RX500736.008, manufactured at a different site (b) (4) than proposed for production (b) (4) met the stability specification for bacterial endotoxins and sterility after storage for (b) (4) months. These batches were all produced with a concentration of 2.5 mg/mL and filled in 2 mL vials.

Reviewer's Assessment: Adequate

Data supports microbiological stability of the drug product for the proposed (b) (4) months.

A Appendices

A.2 Adventitious Agents Safety Evaluation

A.2.1 Materials of Biological Origin

A.2.2 Testing at Appropriate Stages of Production

A.2.3 Viral Testing of Unprocessed Bulk

A.2.4 Viral Clearance Studies

Reviewer's Assessment: N/A

R Regional Information

Executed Batch Records

Batch #(s): 00001, 00002 and 00004, manufactured (b) (4)

Reviewer's Assessment: Adequate

Notes to reviewer:

1. The translated executed batch records (11/10/17 amendment, in English) are blank, except for a few handwritten notes; they appear to reflect the equipment and overall manufacturing set up for commercial production. These records were provided in Italian in the original submission.
2. The proposed Master Batch Record for (b) (4) is not provided.
3. Batch #00003 had an issue with drug product yield and is not used for further testing.

Comparability Protocols

Reviewer's Assessment: N/A. No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

Package Insert

Storage: 20-25°C (68-77°F). Protect from light.
Route of administration: IV

Container: Single dose

- **Post-dilution/constitution hold time**: Dilution of the drug product is not required. No post-dilution storage hold time is noted in the labeling.

Reviewer's Assessment: Adequate

The labeling information is satisfactory related to sterility assurance.

Notes to reviewer:

1. The vial and carton labels indicate single use, sterile and discard unused portion.
2. IRs were sent to the sponsor on November 17, 2017 and March 20, 2018 regarding post-dilution storage times and labeling. Discussion with the sponsor continued after responses received by email November 21, 2017 and in the 1/30/18 and 4/3/18 amendments. In the 4/23/18 amendment, the sponsor noted that there are no plans to perform post-dilution microbiological studies and revised the package insert labeling to remove any reference to use of the product after dilution.

Post-Approval Commitments
Reviewer's Assessment: N/A

***List of Deficiencies*: None**

Primary Microbiology Reviewer Name and Date: Peggy Kriger, Ph.D., 5/8/18

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Erika Pfeiler, Ph.D., 5/8/18

Peggy Kriger

Digitally signed by Peggy Kriger
Date: 5/10/2018 09:44:59AM
GUID: 534c169d00067f29cedbaa415df21ba2

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 5/10/2018 09:46:31AM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 209510

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation, Process Parameters	M	(b) (4)		None
pH	API Solubility, particle size	M			None
Bioburden	Manufacturing evvironment and processes	M			None
Sterility	Sterilization	M			None