APPLICATION NUMBER:

209510Orig1s000

OTHER REVIEW(S)
Memorandum

Date: January 29, 2020

To: Mary Chung, Regulatory Project Manager, (DGIEP)
Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for BARHEMSYS (amisulpride) injection, for intravenous use

NDA: 209510

In response to DGIEP’s consult request dated October 22, 2019, OPDP has reviewed the proposed product labeling (PI) for the original NDA for Barhemsys.

PI: OPDP’s comments on the proposed labeling are based on the draft PI received by electronic mail from DGIEP on January 27, 2020, and are provided below. Please see Table 4 of the PI for our comment.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.
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/s/

MEETA N PATEL
01/29/2020 12:02:40 PM
Memorandum

Date: January 24, 2020

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products / CDER

To: Mary Chung, RPM
DGEIP

Subject: QT-IRT Consult to NDA # 209510 (SDN # NA)

**QT-IRT Responses**

This memo is an addendum to our previous review based on your request (dated 1/23/2020) for additional predictions at different amisulpride concentrations (Table 1). These concentrations were provided by Clinical Pharmacology team.

<table>
<thead>
<tr>
<th>ECG parameter</th>
<th>Treatment (Amisulpride infusion)</th>
<th>Concentration (ng/mL)</th>
<th>∆∆QTcF (msec)</th>
<th>90% CI (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>10 mg dose; over 1 min infusion</td>
<td>451</td>
<td>13.4</td>
<td>(11.7 to 15.1)</td>
</tr>
<tr>
<td>QTc</td>
<td>10 mg dose; over 1 min infusion</td>
<td>140.0</td>
<td>4.9</td>
<td>(3.9 to 6.0)</td>
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<tr>
<td>QTc</td>
<td>10 mg dose; over 1 min infusion</td>
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<td>2.8</td>
<td>(2.0 to 3.7)</td>
</tr>
<tr>
<td>QTc</td>
<td>10 mg dose; over 1 min infusion</td>
<td>68.0</td>
<td>2.0</td>
<td>(1.3 to 2.9)</td>
</tr>
<tr>
<td>QTc</td>
<td>10 mg dose; over 1 min infusion</td>
<td>43.0</td>
<td>0.9</td>
<td>(0.2 to 1.8)</td>
</tr>
<tr>
<td>QTc</td>
<td>10 mg dose; over 1 min infusion</td>
<td>34.0</td>
<td>0.5</td>
<td>(-0.2 to 1.4)</td>
</tr>
</tbody>
</table>

*Source: Predicted based on an Emax model as described in our review of thorough QT study (Dt: 01/12/2018).*

As described in our previous review, the QTc effects of amisulpride were not appropriately characterized in the Sponsor’s study # DP10022 (CS-IRT Review Dr: 12/16/2019). The effect of intravenous administration of amisulpride on the QTc interval was adequately characterized in a thorough QT study (Study # DP10013). For this purpose, we used model described in our previous
review for the above predictions (CS-IRT Review Dt: 01/12/2018). We would like to highlight that the non-linear model was considered appropriate to describe the concentration-QT data and it was also noticed that amisulpride exhibits hysteresis when administered as a 1 min infusion.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov.
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/s/

GIRISH K BENDE  
01/24/2020 01:53:40 PM

CHRISTINE E GARNETT  
01/24/2020 01:54:52 PM
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 23, 2020
Requesting Office or Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number: NDA 209510
Product Name and Strength: Barhemsys (amisulpride) injection, 5 mg/2 mL (2.5 mg/mL)
Applicant/Sponsor Name: Acacia Pharma
OSE RCM #: 2017-1555-4
DMEPA Safety Evaluator: Sarah K. Vee, PharmD
DMEPA Team Leader (Acting): Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM
The Applicant submitted revised container label and carton labeling received on January 15, 2020 for Barhemsys. Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the revised container label and carton labeling for Barhemsys (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review. In addition the Applicant confirmed that they will use a YYYY-MM format for the expiration date on the container label and carton containing one vial and a YYYY-MM-DD format on the outer carton containing ten vials.

2 CONCLUSION
The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

Reference ID: 4550406

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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a Vee S. Label and Labeling Review for Barhemsys (NDA 209510). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 02. RCM No.: 2017-1555-3.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH K VEE
01/23/2020 09:19:14 AM

ASHLEIGH V LOWERY
01/23/2020 09:46:44 AM
Date: December 16, 2019

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiovascular and Renal Products / CDER

To: Mary Chung, RPM
DGEIP

Subject: QT Consult to NDA # 209510 (SDN # 047) & IND # 114207

Note: Any text in the review with a light background should be inferred as copied from the sponsor’s document.

This memo responds to your consult to us dated 9/13/2019 regarding the sponsor’s QT study report (#DP10022). We reviewed the following materials:

- Previous QT-IRT review for IND # 114207 dated 11/15/2012 in DARRTS (link);
- Previous QT-IRT review for IND # 114207 dated 08/26/2013 in DARRTS (link);
- Previous QT-IRT review for IND # 114207 dated 08/10/2015 in DARRTS (link);
- Previous QT-IRT review for IND # 114207 dated 03/20/2017 in DARRTS (link);
- Previous QT-IRT review for NDA # 209510 dated 01/12/2018 in DARRTS (link);
- Previous QT-IRT review for NDA # 209510 dated 05/10/2018 in DARRTS (link);
- Sponsor’s clinical study report # DP10022 (SN0066 / SDN067; link);
- Sponsor’s clinical study safety report # DP10022 (SN0067 / SDN068; link);
- Sponsor’s propose product label (SN0047 / SDN001; link);
- Investigator’s brochure Ed 8.1 (SN0062 / SDN063; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0067 / SDN068; link).

1 Summary

Study # DP10022 is not a thorough QT (TQT) study and the QTc effects are not appropriately characterized. The effect of intravenous administration of amisulpride on the QTc interval was adequately characterized in a TQT study (Study # DP10013). We previously reviewed the study and proposed
to describe the results of the TQT study in the product label (Dt: 01/12/2018; 05/10/2018) with an updated QTc prediction based on the Cmax for the proposed dosing regimen (10 mg dose infused over 1 minute) in the revised product label (Table 1).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for amisulpride (FDA analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Concentration</th>
<th>ΔΔQTcF (msec)</th>
<th>90% CI (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg over 1 min</td>
<td>451 ng/mL</td>
<td>13.4</td>
<td>(11.7 to 15.1)</td>
</tr>
</tbody>
</table>

Source: Predicted based on an Emax model as described in our review of thorough QT study (Dt: 01/12/2018)

The objective of Study # DP10022 was to characterize the effect of intravenous amisulpride (2.5 mg/mL over 1 min, bolus; with and without ondansetron) on the QTc interval using concentration-QTc analysis. Study # DP10022 was a randomized, double-blind, placebo-controlled, (3-period, 3-Sequence) study. The highest dose was 10 mg (administered as intravenous infusion over 1 min) followed by second identical infusion 2 h later. The product was also administered with ondansetron (4 mg over 1 min). The main limitation of the design is it did not include a positive control or had a sufficiently large exposure margin to waive the requirement for a positive control per ICH E14 Q&A (R3) section 5.1. The study protocol and analysis plan were not submitted for our review. In addition, there was a delay observed between peak amisulpride concentration and maximum increase in the QTc interval (Figure 2). The sponsor’s analysis did not account for this delay which will negatively bias the slope of the concentration-QTc relationship and result in an underprediction of the increase in QTc. Furthermore, the sponsor’s analysis used a linear pharmacodynamic model when an Emax model is more appropriate. The present study results are discordant with the previously reviewed thorough QT study (Study # DP10013). Figure 3 presents a comparison of the concentration-QTc relationship obtained from the TQT study (# DP10013) and the current study.

2 Proposed Label

Our changes are highlighted (addition, deletion). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division, including whether or not Section 7.2 is needed since the information is contained in Section 5.1.

5.1 QT Prolongation

BARHEMSYS causes dose- and concentration-dependent prolongation of the QT interval [see Clinical Pharmacology (12.2)].

ECG monitoring is recommended in patients with medical conditions known to prolong the QT interval. [see Drug Interactions (7.2)].

7.2 Drugs Prolonging the QT Interval

BARHEMSYS causes dose-dependent QT prolongation. Because of potential additive effects, ECG monitoring is recommended in patients taking drugs known to prolong the QT interval [see Warnings and Precautions (5.1)].
12.2 Pharmacodynamics

**Cardiac Electrophysiology**

In 40 healthy Caucasian and Japanese subjects, the maximum mean difference (95% upper confidence bound) in QTcF from placebo after baseline-correction (ΔΔQTcF) was 5.0 (7.1) milliseconds after a 2-minute intravenous infusion of 5 mg BARHEMSYS and 23.4 (25.5) milliseconds after an 8-minute intravenous infusion of 40 mg BARHEMSYS [see Warnings and Precautions (5.1)]. A significant exposure-response relationship was identified between amisulpride concentration and ΔΔQTcF. Using this exposure-response relationship, 10 mg infused intravenously over 1 min has a maximal predicted (95% upper prediction interval) ΔΔQTcF of 13.4 (15.1) ms.

The recommended infusion rate is 1 to 2 minutes for 5 mg or 10 mg of BARHEMSYS [see Dosage and Administration (2.1)].

3 Background

3.1 Product Information

Acacia Pharma Inc is developing amisulpride (Barhemsys®; MW: 369.48 g/mol) for the prevention of postoperative nausea and vomiting with or without other antiemetic of a different class and treatment of postoperative nausea and vomiting in patients who have received antiemetic prophylaxis. The product is also being developed for prevention of nausea and vomiting associated with cancer chemotherapy. Amisulpride is a selective dopamine-2 (D2; located in the chemoreceptor trigger zone) and dopamine-3 (D3; in the area postrema) receptor antagonist. It has been approved for oral administration for more than 25 years in ex-US markets (EU; since 1986, maximum doses of 1200 mg/day) and also for intramuscular administration in France (maximum doses of 400 mg/day).

The product is formulated as a sterile solution (amisulpride; 2.5 mg/mL; 5 mg amisulpride in 2 mL vial) for intravenous administration. An oral formulation is also being evaluated for prevention of nausea and vomiting associated with cancer chemotherapy (APD403). The maximum proposed dose is 10 mg (for treatment) to be administered as a single intravenous infusion over 1 to 2 minutes at the time of induction of anesthesia. The peak concentrations of 451 ± 230 ng/mL amisulpride are expected with the maximum therapeutic dose (10 mg infusion over 1 min) at steady-state in healthy subjects. Similarly, the peak concentrations of 285 ± 446 ng/mL amisulpride are expected with the maximum therapeutic dose (10 mg infusion over 1 to 2 min) at steady-state in patients.

The mean elimination half-life is approximately 4 to 5 hours and similar between healthy subjects and surgical patients. In a mass balance study, no metabolites were detectable in plasma while four metabolites were identified in urine and feces. The sponsor claims that amisulpride has low drug interaction potential. Following intravenous administration of amisulpride, 74% and 23% of the administered dose was recovered in urine and feces, respectively. Although the pharmacokinetics of amisulpride in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) have not
been adequately studied, the exposures of amisulpride are expected to be increased in these patient population. Based on the hERG IC50 (44 µM) values, approximately 42-fold margin is expected at the peak concentrations of 451 ng/mL (free 380 ng/ml; 16% protein binding) and suggests the potential for clinical QTc prolongation. Please note, there was a typographical mistake about the reported hERG margin in our previous assessment (Dt: 01/12/2018).

During the development, the QT-IRT reviewed sponsor’s thorough QT study protocol (Dt: 11/15/2012) and its revised version (Dt: 08/26/2013) and commented that the selected doses in the study were not clearly justified (see below). The Sponsor requested if another thorough QT study would be necessary to evaluate the QTc prolongation for ondansetron and amisulpride administered sequentially. Based on the known QTc prolongation associated with ondansetron administration along with the planned thorough QT study for amisulpride in 2015, the QT-IRT responded that a specific thorough QT study is not necessary. However, the intensive ECG monitoring was recommended for future studies (Dt: 08/10/2015). Subsequently, the sponsor requested information on if the results of their thorough QT study would be adequate prior to submitting the study data to the QT-IRT. The QT-IRT responded that they cannot agree until the study data and concentration-QTc analysis has been submitted and reviewed. (Dt: 03/20/2017).

Subsequently, the QT-IRT reviewed the sponsor’s thorough QT study (Study # DP10013) assessing the effect of intravenous amisulpride on QTc interval as compared to placebo and moxifloxacin in healthy adult subjects (n=40). This was a randomized, double-blind, placebo- and positive-controlled, (4-period, 4-sequence) crossover study. The subjects were randomized to receive 1) amisulpride 5 mg over 2 min (therapeutic dose), 2) amisulpride 40 mg over 8 min (supra-therapeutic dose), 3) placebo, and 4) a single oral dose of moxifloxacin 400 mg (open-label) with a washout period (≥ 7 days). The non-linear (Emax) model was considered appropriate to describe the observed concentration-QTc relationship for amisulpride. The peak concentrations observed at supratherapeutic dose offered ~3.8-fold margin over those expected with the highest recommended therapeutic dose and were expected to cover the worst-case scenario (renal impairment). Since the highest recommended therapeutic dose (10 mg infused over 4 min) was not included in the study, the model predicted effects (ΔΔQTcF of 11.2 ms; 90%CI upper: 12.6 ms) were used for analysis. Thus, the QT-IRT’s assessment concluded that amisulpride prolongs the QTc interval in a concentration-dependent manner (Dt: 01/12/2018 & 05/10/2018).

Recently, the sponsor conducted additional QT study (Study # DP10022; NCT03583489) assessing the effect of intravenous amisulpride (2.5 mg/mL; with and without ondansetron) on QTc interval in healthy adult subjects using concentration-QTc analysis (see Section 3.2). The objective of the analysis was to assess the relationship between amisulpride concentration and QTcF. An exploratory evaluation of the time-course of amisulpride concentration and changes in ΔΔQTcF from Study # DP10022 and Study # DP10013 (thorough QT study) is shown in Figure 1. The previous assessment has already confirmed the non-linear relationship (Dt: 03/20/2017). Thus, a linear model was not considered appropriate to describe the relationship between concentration and ΔΔQTcF instead a non-linear (Emax) model was utilized (Figure 2 and Figure 3).

Reference ID: 4534149
Figure 1: Time course of amisulpride concentration (top) and QTc (bottom)
[Study # DP10022 and Study # DP10013]

Source: Reviewer’s analysis
Figure 2: Plasma concentration and ΔΔQTcF Versus Time profile
   [Study # DP10022]

Source: Cardiac Safety Report, Figure 14.2.2.6.1.1

Figure 3: Goodness-of-fit plot for QTc
   [Study # DP10022 (New) and Study # DP10013 (TQT)]

Source: Reviewer’s analysis

Reference ID: 4534149
The maximum concentration of 554 ± 244 ng/mL (n=29; Tmax: ~2 h) were observed with intravenous administration amisulpride (10 mg over 1 min infusion). While, the maximum concentrations of 461 ± 260 ng/mL (n=30; Tmax: ~0.2 h) were observed with intravenous administration amisulpride (10 mg over 1 min infusion) and ondansetron. The present study (Study # DP10022) neither included a positive control nor had an exposure margin considered sufficiently large to waive the requirement for a positive control for assay sensitivity.

3.2 Sponsor’s position related to the question

The sponsor conducted additional QT study (Study # DP10022) assessing the effect of intravenous amisulpride (2.5 mg/mL; with and without ondansetron) on QTc interval in healthy adult subjects using concentration-QTc analysis (primary: ΔΔQTcF). This was a single-center, randomized, double-blind, placebo-controlled, (3-period, 3-Sequence) crossover study using Williams design. The subjects (n=30) were randomized to receive - 1) placebo over 1 min followed by second identical infusion 2 h later, 2) amisulpride 10 mg over 1 min, followed by second identical infusion 2 h later, and 3) amisulpride 10 mg over 1 min plus simultaneous infusion of ondansetron 4 mg, over 1 min; followed by placebo infusion 2 h later (drug interaction), with a washout period (≥ 2 days). Based on the tolerability, the rate of infusion was to be reduced such that the total time for the infusion was up to 4 min. This protocol was not reviewed by the QT-IRT previously.

The sponsor’s concentration analysis (Figure 4) claims that the mean maximal ΔΔQTcF of an initial 10 mg dose of amisulpride administered alone was 5.2 ms (90% CI: 3.53; 6.96), occurring at 10 min post-dose. The mean maximal ΔΔQTcF of a second 10 mg dose of amisulpride administered 2 h after the first was 8.0 ms (90% CI: 5.49; 10.58), also occurring at 10 min post-dose. The upper bound of the 90% CI did not exceed the ICH threshold of concern of 10 ms after the initial infusion. After the second infusion, the upper bound was marginally above 10 ms, but for not more than 10 minutes.
Reviewer’s Comments: The sponsor observed delayed QTc effects associated with rapid intravenous administrations (over 1 min; bolus) of amisulpride. The sponsor’s analysis did account for the hysteresis which resulted in a negatively biased slope and underprediction of drug effects. Furthermore, the sponsor used a linear model when the relationship is nonlinear. Moreover, these results are discordant with the previously reviewed thorough QT study (Study # DP10013).

3.3 Nonclinical Cardiac Safety
Refer to highlights of clinical pharmacology and cardiac safety.

3.4 Clinical Cardiac Safety
Refer to highlights of clinical pharmacology and cardiac safety.

3.5 Summary results of prior QTc assessments
Refer to previous QT-IRT reviews for NDA-209510 dated 01/12/2018 and its addendum dated 05/10/2018 in DARRTS. The QT-IRT’s assessment concluded that amisulpride exhibits QTc interval prolongation in a concentration-dependent manner (Dt: 01/12/2018 & 05/10/2018).
3.6 Relevant details of planned Phase 3 study
Based on the thorough QT study results, the sponsor was previously informed that the intensive ECG monitoring would be necessary in future clinical studies.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqqt@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GIRISH K BENDE  
12/16/2019 08:32:26 AM

LARS JOHANNESEN  
12/16/2019 08:36:04 AM

CHRISTINE E GARNETT  
12/16/2019 08:42:27 AM
**Date of This Review:** December 2, 2019

**Requesting Office or Division:** Division of Gastroenterology and Inborn Errors Products (DGIEP)

**Application Type and Number:** NDA 209510

**Product Name, Dosage Form, and Strength:** Barhemsys (amisulpride) injection, 5 mg/2 mL (2.5 mg/mL)

**Product Type:** Single Ingredient Product

**Rx or OTC:** Prescription (Rx)

**Applicant/Sponsor Name:** Acacia Pharma

**FDA Received Date:** August 26, 2019

**OSE RCM #:** 2017-1555-3

**DMEPA Safety Evaluator:** Sarah K. Vee, PharmD

**DMEPA Team Leader:** Idalia E. Rychlik, PharmD
1 REASON FOR REVIEW
As part of the approval process for Barhemsys (amisulpride) injection, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Barhemsys prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY
NDA 209510 was first submitted on October 5, 2017 and received a complete response (CR) on October 5, 2018. Acacia Pharma submitted a response to the CR on November 5, 2018 and received a second CR on May 2, 2019. Thus, Acacia Pharma submitted a response to the second CR on August 26, 2019. We reviewed the PI, container label, and carton labeling during the previous review cycles (see Appendix B).

3 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>N/A</td>
</tr>
<tr>
<td>ISMP Newsletters*</td>
<td>N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>N/A</td>
</tr>
<tr>
<td>Other</td>
<td>N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>C</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
Acacia Pharma submitted a second response to a CR for NDA 209510 (Barhemsys (amisulpride)). We reviewed the prescribing information, carton labeling, and container label. Since the last review, the Applicant revised the PI and proposed to (b) (4) . We defer the acceptability of these revisions to DGIEP. The Applicant also made minor editorial changes to the carton labeling and container label (e.g., Changed "TM" to registered mark: * ). We identified areas in the Barhemsys container label and carton labeling that can be improved to increase readability and prominence of important information.
5 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendation in Section 5.1 for the Applicant.

5.1 RECOMMENDATIONS FOR ACACIA PHARMA

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Carton Labeling

1. To ensure consistency with the Prescribing Information, revise the statement, "Recommended Dosage: See prescribing information."

C. Container Label

1. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is in close proximity to the strength statement.

2. Combine the statements “single-dose sterile vial” and “Discard Unused Portion” into one line.

3. As currently presented the expiration statement, (b)(4) is incomplete and may cause confusion, remove the statement.
Table 2. Relevant Product Information for Barhemsys

<table>
<thead>
<tr>
<th>Initial Approval Date</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>amisulpride</td>
</tr>
</tbody>
</table>
| **Indication**        | • Prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class.  
                          • Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or who have not received prophylaxis. |
| **Route of Administration** | Intravenous injection |
| **Dosage Form**       | Injection |
| **Strength**          | 5 mg/2 mL (2.5 mg/mL) |
| **Dose and Frequency**| • Prevention of PONV, either alone or in combination with another antiemetic: 5 mg as a single intravenous dose infused over 1 to 2 minutes at the time of induction of anesthesia.  
                           • Treatment of PONV: 10 mg as a single intravenous dose infused over 1 to 2 minutes. |
| **How Supplied**      | Package of 10 cartons. Each carton (NDC 71390-125-21) contains one single-dose vial of clear, colorless, and sterile solution of BARHEMSYS (amisulpride) injection, 5 mg in 2 mL (2.5 mg/mL). |
| **Storage**           | Store vials at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].  
                           Protect from light. Administer BARHEMSYS within 12 hours after the vial is removed from the protective carton |
APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 13, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, amisulpride. Our search identified three previous reviews\(^a\),\(^b\),\(^c\), and we confirmed that our previous recommendations were implemented.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis\(^d\), along with postmarket medication error data, we reviewed the following Barhemsys labels and labeling submitted by Acacia Pharma.

- Container label(s) received on August 26, 2019
- Carton labeling received on August 26, 2019
- Prescribing Information (Image not shown) received on August 26, 2019

C.2 Label and Labeling Images

Container label

\(^a\) Abraham, S. Label and Labeling Review for Barhemsys (NDA 209510). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 06. RCM No.: 2018-1555.

\(^b\) Abraham, S. Label and Labeling Review for Barhemsys (NDA 209510). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 02. RCM No.: 2018-1555-1.


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/s/

SARAH K VEE
12/02/2019 02:00:47 PM

IDALIA E RYCHLIK
12/03/2019 06:29:02 AM

Reference ID: 4527566
Pharmacovigilance Review

Date: November 13, 2019

Reviewer: Michelle Hines, PharmD
Division of Pharmacovigilance I (DPV-I)

Team Leader (Acting): Paolo Fanti, MD
DPV-I

Deputy Division Director: Monica Muñoz, PharmD, PhD, BCPS
DPV-I

Product Name: Barhemsys (amisulpride injection)

Subject: All adverse events

Application Type/Number: NDA 209510

Applicant: Acacia Pharma Ltd.

OSE RCM #: 2019-1961
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1 INTRODUCTION

This review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology and Inborn Errors Products (DGIEP), contains an evaluation of the FDA Adverse Event Reporting System (FAERS) database for all adverse events with amisulpride through October 8, 2019. This review will inform DGIEP as they determine the acceptability of product labeling submitted for NDA 209510 Barhemsys (amisulpride injection).

1.1 BACKGROUND AND REGULATORY HISTORY

Amisulpride is a selective dopamine-2 (D₂) and dopamine-3 (D₃) receptor antagonist; D₂ receptors in the chemoreceptor trigger zone (CTZ) and D₃ receptors in the area postrema play a role in emesis.¹ Amisulpride has low affinities for the 5-HT₂B and 5-HT₇ receptors, and no appreciable affinity for any other receptor types. Amisulpride was first approved for use in 1986 in Europe and is now licensed in over 50 countries worldwide as an atypical antipsychotic treatment for acute and chronic schizophrenia.² When used as an antipsychotic, amisulpride is primarily administered as an oral tablet or solution but is also available for intramuscular administration.

On August 3, 2017, the applicant submitted NDA 209510 proposing the use of amisulpride injection for the following indications: 1) the prevention of postoperative nausea and vomiting (PONV), either alone or in combination with other antiemetics; and 2) treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis. The proposed dosage of amisulpride injection is a single intravenous (IV) administration of 5 milligrams (mg) for PONV prophylaxis given at the time of anesthesia induction, or a single IV administration of 10 mg to treat an episode of PONV.

On October 5, 2018, FDA issued a complete response (CR) for NDA 209510; the main CR issue was facility inspection deficiencies. On May 2, 2019, FDA issued a second CR for NDA 209510 because the facility issues were not adequately addressed.

On August 26, 2019, the applicant resubmitted NDA 209510 to FDA. The proposed labeling for amisulpride injection contains a Postmarketing Experience section that lists adverse events that were identified from postmarketing, chronic, oral use of amisulpride outside of the United States. To support the postmarketing safety experience of amisulpride, the applicant provided an assessment of postmarketing adverse event reports with amisulpride within the European Medicines Agency’s Eudravigilance database from 2003 to 2017. Of 2,765 adverse event reports with amisulpride in the Eudravigilance database, 165 had interpretable cumulative dose information. FDA completed a multidisciplinary review and evaluation of NDA 209510 amisulpride injection on October 5, 2018, that included an assessment of the postmarketing safety data for amisulpride that the applicant provided; portions of FDA’s assessment of these data are reproduced below:

“The most common adverse events (AEs) reported are those that would be expected with a dopamine antagonist. In addition, given the known risk of QT prolongation, it is not surprising
that QT prolongation was seen, as well as the subsequent clinical occurrences that could occur with doses exceeding the recommended daily oral dose.

In contrast, IV amisulpride is proposed as a single dose, for inpatient treatment. The proposed labeling adequately communicates the potential risks regarding QT prolongation. In addition, IV amisulpride will only be administered in the operating room and/or post-anesthesia care unit. Patients will be uniquely located in the hospital’s most acute care setting wherein they will receive intensive monitoring. Thus, it is unlikely that many of the reactions which are typically seen with chronic oral use will occur.”

On September 20, 2019, DGIEP consulted DPV-I to assist with the labeling review of the proposed Postmarketing Experience section of the amisulpride injection package insert.

1.2 APPLICANT’S PROPOSED LABELING FOR AMISULPRIDE INJECTION FROM AUGUST 26, 2019

The WARNINGS AND PRECAUTIONS and Postmarketing Experience sections of the most recent version of the applicant’s proposed labeling for amisulpride injection, which was submitted to FDA on August 26, 2019, are reproduced below.

5 WARNINGS AND PRECAUTIONS
5.1 QT Prolongation
BARHEMSYS causes dose-dependent prolongation of the QT interval. The recommended dosage of 5 or 10 mg as a single intravenous dose infused over 1 to 2 minutes, prolongation of the QT interval was less than 10 milliseconds [see Clinical Pharmacology (12.2)].

ECG monitoring is recommended in patients with

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval chronic oral use of amisulpride outside of the United States (BARHEMSYS is not approved for oral dosing or chronic use). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Blood and lymphatic system disorders**: agranulocytosis,
- **Cardiac disorders**: bradycardia, torsades de pointes, ventricular tachycardia, prolonged QT by electrocardiogram
- **General disorders**: neuroleptic malignant syndrome
- **Immune system disorders**: angioedema, hypersensitivity, urticaria
- **Hepatic disorders**: increased hepatic enzymes
- **Nervous system disorders**: agitation, anxiety, dystonia, extrapyramidal disorder, seizure
- **Psychiatric disorders**: confusional state, insomnia, somnolence
2 METHODS AND MATERIALS

2.1 FAERS DATABASE

DPV-I searched the FAERS database with the strategy described in Table 1.

<table>
<thead>
<tr>
<th>Table 1. FAERS Search Strategy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of search</td>
</tr>
<tr>
<td>Time period of search</td>
</tr>
<tr>
<td>Search type</td>
</tr>
<tr>
<td>Product Active Ingredients</td>
</tr>
</tbody>
</table>

* See Appendix A for a description of the FAERS database.

2.2 CAUSALITY ASSESSMENT

We assessed adverse events identified from our search of the FAERS database (described in Table 1) for a causal relationship with amisulpride using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system as shown below in Table 2.

| Table 2. Causality Classification and Criteria Based on the WHO-UMC System |
|---------------------|--------------------------------------------------------------------------|
| Causality Term      | Assessment Criteria                                                                 |
| Certain             | • Event or laboratory test abnormality, with plausible time relationship to drug intake |
|                     | • Cannot be explained by disease or other drugs                             |
|                     | • Response to withdrawal plausible (pharmacologically, pathologically)      |
|                     | • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) |
|                     | • Rechallenge satisfactory, if necessary                                   |
| Probable            | • Event or laboratory test abnormality, with reasonable time relationship to drug intake |
|                     | • Unlikely to be attributed to disease or other drugs                       |
|                     | • Response to withdrawal clinically reasonable                              |
|                     | • Rechallenge not required                                                  |
| Possible            | • Event or laboratory test abnormality, with reasonable time relationship to drug intake |
|                     | • Could also be explained by disease or other drugs                         |
|                     | • Information on drug withdrawal may be lacking or unclear                  |
| Unlikely            | • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) |
|                     | • Disease or other drugs provide plausible explanation                      |
| Unassessable        | • Report suggesting an adverse reaction                                     |
|                     | • Cannot be judged because information is insufficient or contradictory     |
|                     | • Data cannot be supplemented or verified                                   |
3 RESULTS

3.1 FAERS DATABASE

Our search of the FAERS database described in Table 1 yielded 2,236 reports. We did not perform case-level analysis on all reports. Report counts may include duplicate reports for the same patient from multiple reporters, miscoded reports, or unrelated reports.

Table 2 lists descriptive characteristics of adverse events with amisulpride that were reported to the FAERS database.

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>976</td>
<td>1,048</td>
<td>212</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to &lt;17 years</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 to &lt;65 years</td>
<td>1,534</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>267</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>394</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign</td>
<td>2,190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Report type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expedited</td>
<td>2,192</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periodic</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious outcomes†</td>
<td>(n=2,211)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>276</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1,209</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening</td>
<td>232</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other serious outcome</td>
<td>1,254</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* May include duplicates
† Per 21 CFR 314.80, a serious adverse drug experience includes outcomes of: death, life-threatening, hospitalization, disability, congenital anomaly, and other serious important medical events. A report can have one or more outcomes.

DPV compared each term to the applicant’s proposed labeling for amisulpride injection that was submitted to FDA on August 26, 2019. Table 3 lists the 50 most frequently reported PTs for amisulpride, which encompassed 1,697 of 2,236 (76 percent) total adverse event reports with
amisulpride, for each event.

The postmarketing reports in the FAERS database involve chronic amisulpride use for schizophrenia or other psychiatric disorders; most reports indicated that the patient was taking multiple concomitant antipsychotic/psychiatric medications.a

Table 3. Most Frequently Reported MedDRA PTs with Amisulpride, Received by FDA Through October 8, 2019 (n=1,697)

<table>
<thead>
<tr>
<th>MedDRA PT</th>
<th>Number of Reports*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug interaction†</td>
<td>208</td>
</tr>
<tr>
<td>Drug ineffective</td>
<td>193</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
<td>150</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>131</td>
</tr>
<tr>
<td>Toxicity to various agents†</td>
<td>123</td>
</tr>
<tr>
<td>Weight increased†</td>
<td>110</td>
</tr>
<tr>
<td>Overdose</td>
<td>103</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>103</td>
</tr>
<tr>
<td>Suicide attempt†</td>
<td>101</td>
</tr>
<tr>
<td>Extrapyramidal disorder</td>
<td>90</td>
</tr>
<tr>
<td>Fall†</td>
<td>90</td>
</tr>
<tr>
<td>Condition aggravated</td>
<td>85</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>85</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>84</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>84</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>82</td>
</tr>
<tr>
<td>Confusional state</td>
<td>80</td>
</tr>
<tr>
<td>Intentional overdose</td>
<td>79</td>
</tr>
<tr>
<td>Tremor†</td>
<td>79</td>
</tr>
<tr>
<td>Vomiting†</td>
<td>77</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased†</td>
<td>76</td>
</tr>
<tr>
<td>Blood prolactin increased</td>
<td>71</td>
</tr>
<tr>
<td>Aggression†</td>
<td>70</td>
</tr>
<tr>
<td>Hallucination, auditory†</td>
<td>70</td>
</tr>
<tr>
<td>Hypotension</td>
<td>70</td>
</tr>
<tr>
<td>Agitation</td>
<td>66</td>
</tr>
<tr>
<td>Somnolence</td>
<td>65</td>
</tr>
<tr>
<td>Pyrexia†</td>
<td>63</td>
</tr>
<tr>
<td>Akathisia</td>
<td>62</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>60</td>
</tr>
<tr>
<td>Sedation</td>
<td>60</td>
</tr>
</tbody>
</table>

a Of note, 749 of 2,239 total reports (33 percent) had concomitant clozapine.
## Table 3. Most Frequently Reported MedDRA PTs with Amisulpride, Received by FDA Through October 8, 2019 (n=1,697)

<table>
<thead>
<tr>
<th>MedDRA PT</th>
<th>Number of Reports*</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count increased†</td>
<td>59</td>
</tr>
<tr>
<td>Suicidal ideation†</td>
<td>57</td>
</tr>
<tr>
<td>Rhabdomyolysis†</td>
<td>56</td>
</tr>
<tr>
<td>Constipation†</td>
<td>55</td>
</tr>
<tr>
<td>Acute kidney injury†</td>
<td>53</td>
</tr>
<tr>
<td>Product use in unapproved indication</td>
<td>52</td>
</tr>
<tr>
<td>Coma†</td>
<td>51</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>50</td>
</tr>
<tr>
<td>Hyponatraemia†</td>
<td>49</td>
</tr>
<tr>
<td>Treatment noncompliance</td>
<td>48</td>
</tr>
<tr>
<td>Anxiety</td>
<td>47</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>47</td>
</tr>
<tr>
<td>Depression†</td>
<td>46</td>
</tr>
<tr>
<td>Intentional self-injury†</td>
<td>46</td>
</tr>
<tr>
<td>Pneumonia†</td>
<td>46</td>
</tr>
<tr>
<td>Tardive dyskinesia§</td>
<td>44</td>
</tr>
<tr>
<td>Depressed level of consciousness†</td>
<td>43</td>
</tr>
<tr>
<td>Off label use</td>
<td>43</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>42</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
<td>42</td>
</tr>
<tr>
<td>Platelet count decreased†</td>
<td>42</td>
</tr>
<tr>
<td>Sopor</td>
<td>42</td>
</tr>
</tbody>
</table>

† DPV-I performed hands-on review of 20 percent of reports with this PT.
‡ The reports of rhabdomyolysis or increased creatine phosphokinase (CPK) that DPV-I reviewed had concomitant medications or disease states that can contribute to rhabdomyolysis or increased CPK; DPV-I did not identify any reports that described the occurrence of these events following a single dose of amisulpride.
§ The term tardive dyskinesia implies long-term use of a medication, which is not applicable to the proposed indication of PONV for amisulpride. “Extrapyramidal disorder” is listed in the proposed Postmarketing Experience section.

We were able to evaluate the amisulpride dosage for 829 of 2,239 reports; of these, 7 unique reports listed amisulpride doses less than 50 mg. The dosing regimens for these 7 reports are summarized below:

- 25 mg once daily (n=3)
- 25 mg twice daily (n=1)
- 25 mg (frequency not reported) (n=1)
- 30 mg (frequency not reported) (n=1)
- 40 mg (frequency not reported) (n=1)

Of the seven reports with amisulpride doses less than 50 mg, the adverse events in six can be attributed to either amisulpride or concomitant antipsychotic medications (n=5) or
benzodiazepines (n=1), and the adverse events in one report have an unlikely causal association to amisulpride (patient had taken amisulpride for years and experienced the reported events on the same day of initiating antihypertensive medication).

We did not identify any reports that were coded with IV administration for amisulpride.

4 DISCUSSION

This review, completed by DPV-I in response to a consult from DGIEP, contains an evaluation of the FAERS database for all adverse events with amisulpride through October 8, 2019. This review will inform DGIEP as they determine the acceptability of product labeling submitted for NDA 209510 Barhemsys (amisulpride injection).

The proposed Postmarketing Experience section for amisulpride injection that was submitted to FDA on August 26, 2019, lists adverse events that were identified from postmarketing, chronic, oral use of amisulpride outside of the United States. Similarly, postmarketing adverse event reports in the FAERS database reflect chronic amisulpride use for schizophrenia or other psychiatric disorders.

DPV-I reviewed the 50 most frequently reported PTs with amisulpride and did not identify any potential safety signals for single 5- or 10-mg doses of amisulpride injection that are not listed in the applicant’s proposed labeling. Postmarketing reports with amisulpride in the FAERS database have limited utility to inform the safety of amisulpride injection for PONV because these reports describe adverse events with chronic use of amisulpride at higher doses than proposed for the treatment of PONV. Furthermore, most FAERS reports with amisulpride indicated that the patient was taking multiple concomitant antipsychotic/psychiatric medications; notably, 749 of 2,239 total reports (33 percent) had concomitant clozapine. The clozapine labeling includes boxed warnings (e.g., neutropenia, [orthostatic] hypotension, bradycardia, seizure) or warnings (e.g., QT interval prolongation, hyperglycemia, dyslipidemia, neuroleptic malignant syndrome, [venous] embolism) for several events that are reflected in the 50 most frequently reported PTs with amisulpride or the proposed Postmarketing Experience section of the amisulpride injection labeling. Therefore, some events reflected in the current version of the Postmarketing Experience section may reflect adverse events associated with chronic use of higher amisulpride doses or concomitant medications.

The applicant’s proposed Postmarketing Experience section contains a statement that the adverse reactions listed were associated with chronic oral use of amisulpride outside of the United States. DPV-I was able to evaluate the amisulpride dosage for 829 of 2,239 (37 percent) reports in the FAERS database; of these, 7 listed amisulpride doses less than 50 mg, however none of the 7 had an unlabeled safety signal or informed the safety of amisulpride injection. Therefore, DPV-I agrees that informing providers that events listed in Postmarketing Experience occurred in the context of chronic oral use of amisulpride.
5 RECOMMENDATIONS

DPV-1 provides recommendations that pertain to the Postmarketing Experience section of the applicant’s proposed labeling for amisulpride injection from August 26, 2019.

- The terms that the applicant listed in the proposed Postmarketing Experience section are acceptable and reflect chronic use of oral amisulpride.
6 REFERENCES


2. Introduction (APD421 Solution for Injection). Acacia Pharma Inc.; submitted to FDA on August 3, 2017. Available at \cdsesub1\evsprod\nda2095100001\m2\22-intro\introduction.pdf

7 APPENDIX

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA’s postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHELLE C HINES
11/13/2019 08:59:27 AM

PAOLO FANTI
11/13/2019 10:05:25 AM

MONICA MUNOZ
11/13/2019 10:45:17 AM
MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 2, 2018
Requesting Office or Division: Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number: NDA 209510
Product Name and Strength: Barhemsys (amisulpride) injection
5 mg/2 mL (2.5 mg/mL)
Submission date: September 17, 2018
Applicant/Sponsor Name: Acacia Pharma
OSE RCM #: 2017-1555-1
DMEPA Primary Reviewer: Sherly Abraham, RPh
DMEPA Team Leader: Sarah K. Vee, Pharm.D.

1  PURPOSE OF MEMO
Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the prescribing information (PI), container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review cycle.¹

2  CONCLUSION
We find the PI, container label and carton labeling acceptable from medication error perspective and have no recommendations at this time.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
10/02/2018

SARAH K VEE
10/02/2018
MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 15, 2018

To: Dragos Roman, M.D., Acting Director
Division of Gastroenterology and Inborn Errors of Metabolism

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Amisulpride (tradename: Baremsis)
NDA 209,510 (IND 114,207)
Indication: Postoperative Nausea and Vomiting
Dosage: 5 mg (intravenous)
Sponsor: Acacia Pharma, Ltd.

Materials reviewed: NDA submission (8/3/17)

A. Background

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Controlled Substance Staff (CSS) on July 13, 2018, regarding the abuse potential of intravenous (IV) amisulpride (APD421, tradename: Baremsis) under NDA 209,510 (submitted August 3, 2017). CSS previously consulted on this drug during development under IND 114207.

Amisulpride is a D2/3 receptor antagonist being developed for postoperative nausea and vomiting (PONV). The product is formulated for an intravenous dose of 5 mg. Amisulpride has been evaluated in IV single-dose studies up to 100 mg in healthy volunteers.

Although amisulpride has been approved in Europe and other countries since the 1980s as an oral and intramuscular formulation for treatment of psychoses, it has not been approved previously in the United States. Thus, amisulpride is a new molecular entity in this country. An intravenous formulation of amisulpride is currently not available.
anywhere in the world. Evidence of drug misuse or abuse has not been described in the postmarketing experience or in the published literature.

B. Conclusions

1. Amisulpride is an antagonist at dopamine D2 and D3 receptors. Since euphoria-like responses typically involve the agonism at dopamine receptors, it would be unlikely that a drug that functions as an antagonist at these sites would have abuse potential.

2. An animal self-administration study showed that rats do not self-administer amisulpride at levels above that of vehicle. These data suggest that amisulpride does not have rewarding properties. This is consistent with its action as a dopamine antagonist.

3. The adverse event profile of amisulpride from the clinical studies submitted in the NDA do not suggest that the drug has abuse potential. Amisulpride does not produce any euphoria-like responses in clinical studies. The only CNS-related AEs reported from 5 and 10 mg doses of amisulpride were headache (~4%), dizziness (~2%) and insomnia (~2%).

4. Since amisulpride is proposed for the treatment of PONV, there is no risk of physical dependence.

C. Recommendations

The intravenous drug product containing amisulpride for single-dose administration does not have abuse potential and poses no risk of physical dependence. Thus, CSS recommends that:

1. The drug label for the amisulpride product should not include Section 9 Abuse and Dependence

2. Amisulpride should not be recommended for scheduling under the Controlled Substances Act.

D. Discussion

*Rat Self-Administration Study (Study #13.0123)*

Rats were trained in a self-administration procedure using intravenous cocaine (0.25 mg/kg/infusion). When rats were given access to intravenous amisulpride (0.25 and 1
mg/kg/infusion), they did not self-administer the drug at levels above that shown for vehicle.

**Abuse-Related Adverse Events**

The adverse event profile of amisulpride from the clinical studies submitted in the NDA do not suggest that the drug has abuse potential.

Amisulpride does not produce any euphoria-like responses in clinical studies.

The only CNS-related AEs reported from a 5 and 10 mg dose of amisulpride were headache (~4%), dizziness (~2%) and insomnia (~2%).

**Physical Dependence**

The Sponsor states, “As amisulpride is proposed as a single dose administration only, the risk of withdrawal or rebound effects is considered negligible. There is no evidence in the amisulpride safety database to suggest the occurrence of any withdrawal or rebound phenomena.”
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHERINE R BONSON
08/15/2018

SILVIA N CALDERON
08/15/2018

DOMINIC CHIAPPERINO
08/15/2018
Clinical Inspection Summary

NDA 209510 [amisulpride]

Clinical Inspection Summary

Date | June 7, 2018
---|---
From | Susan Leibenhaut, M.D., OSI/DCCE/GCPAB
 | Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB
 | Kassa Ayalew, M.D., M.P.H., Branch Chief,
 | OSI/DCCE/GCPAB
To | Marjorie Dannis, M.D., Medical Officer, DGIEP
NDA # | 209510
Applicant | Acacia Pharma Ltd.
Drug | amisulpride
NME | Yes
Division Classification | Anti-Emetics/Seratonergics and Others
Proposed Indication | 1. Prevention of Post-Operative Nausea and Vomiting (PONV), either alone or in combination with other antiemetics
 | 2. Rescue treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis
Consultation Request Date | January 8, 2018
Summary Goal Date | June 15, 2018
Action Goal Date | October 5, 2018
PDUFA Date | October 5, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA consisted of inspections of five clinical investigator (CI) sites and the sponsor Acacia Pharma Ltd. Three of the clinical sites and the sponsor have the final or preliminary classification of No Action Indicated (NAI). Two of the clinical sites have the final or preliminary classification of Voluntary Action Indicated (VAI). No significant regulatory findings or data integrity issues were noted.

The data generated by these sites and the sponsor are acceptable in support of the application.
II. BACKGROUND

The sponsor submitted this NDA for the use of APD421 (amisulpride for intravenous [IV] injection) for:

- Prevention of post-operative nausea and vomiting (PONV), either alone or in combination with other antiemetics
- Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis

APD421 is an IV formulation of amisulpride, a potent and selective dopamine D2 and D3 antagonist currently marketed in Europe in oral form as an anti-psychotic. Amisulpride was first licensed in France more than 30 years ago and is now approved in more than 50 countries worldwide, though not the United States of America. It is generally approved for use in psychiatric practice at a dose range between 50 and 1200 mg/day by mouth and, in France, by intramuscular injection.

Drug: amisulpride

Study – Protocol number and title for all studies that were inspected

1. Protocol DP 10015 entitled, “A Randomized, double-blind, placebo-controlled, Phase III study of APD421 (amisulpride for IV injection) as prophylaxis against post-operative nausea and vomiting”

   Number of subjects: 364 subjects
   Number of sites: 8 sites
   Number of countries where subjects were enrolled: U.S. only
   Dates that study was conducted: from August 2013 to January 2014
   Efficacy endpoint: “Complete Response” defined as absence of PONV2 in the period 0-24 hours after the end of surgery (defined as the time of wound closure); specifically, no episodes of vomiting/retching and no use of antiemetic rescue medication in the first 24 hours after surgery

2. Protocol DP 10017 entitled “Randomized, double-blind, placebo-controlled, Phase III study of APD421 (amisulpride for IV injection) as combination prophylaxis against post-operative nausea and vomiting in high-risk patients”

   Number of subjects: 1204 subjects
   Number of sites: 29 sites
   Number of countries where subjects were enrolled: 3
   Dates that study was conducted: February 2015 to September 2015
   Efficacy endpoint: absence or presence of PONV during the 24-hour post-operative period, where PONV was defined as the occurrence of one or more emetic episodes (vomiting or retching)
retching) or the receipt of one or more doses of rescue anti-emetic medication. Absence of PONV by this definition was termed “Complete Response” (CR).

3. Protocol DP 10018 entitled “A randomized, double-blind, placebo-controlled study of APD421 (amisulpride for IV injection) as treatment of established post-operative nausea and vomiting, in patients who have had no prior prophylaxis”

Number of subjects: 1988 subjects
Number of sites: 21 sites
Number of countries where subjects were enrolled: 4
Dates that study was conducted: August 2015 to July 2016
Efficacy endpoint: success or failure of initial PONV treatment, where success is defined as no emetic episodes (vomiting or retching) from 30 minutes to 24 hours after administration of study medication and no administration of anti-emetic rescue medication at any time in the 24-hour period after administration of study medication.

4. Protocol DP 10019 entitled “A Randomized, double-blind, placebo-controlled study of APD421 (amisulpride for IV injection) as treatment of established post-operative nausea and vomiting, in patients who have had prior prophylaxis”

Number of subjects: 1204 subjects
Number of sites: 29 sites
Number of countries where subjects were enrolled: 3
Dates that study was conducted: February 2015 to September 2015
Efficacy endpoint: success or failure of initial PONV treatment, where success is defined as no emetic episodes (vomiting or retching) from 30 minutes to 24 hours after administration of study medication and no administration of anti-emetic rescue medication at any time in the 24-hour period after administration of study medication.

**Rationale for Site Selection:** Sites were chosen based on enrollment, efficacy results, and participation in more than one of the studies.
### III. RESULTS (by site):

<table>
<thead>
<tr>
<th>Name and Type of Inspected Entity/Address</th>
<th>Protocol #/ Site #/ # of Subjects</th>
<th>Inspection Dates</th>
<th>Classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI: Prof Dr Peter Kranke University Hospitals of Würzburg, Department of Anaesthesia and Critical Care Oberdürrbacher Str. 6, 97080 Würzburg, Germany</td>
<td>DP 10018 Site 11 102 subjects</td>
<td>April 9 to 19, 2018</td>
<td>NAI</td>
</tr>
<tr>
<td>CI: Ngai Liu, MD., Ph.D. Hopital FOCH, 40 rue Worth, BP 36,92151 Suresnes Cedex, Paris, France</td>
<td>Protocol DP 10017 Site 707 60 subjects</td>
<td>March 19 to 23, 2018</td>
<td>NAI pending</td>
</tr>
<tr>
<td>CI: David Leiman, M.D. Christus St. John Hospital 18300 St John Dr. Nassau Bay, TX 77058</td>
<td>Protocol DP 10015 Site 503 55 subjects</td>
<td>May 14 to 17, 2018</td>
<td>NAI pending</td>
</tr>
<tr>
<td>CI: Harold Minkowitz, M.D. Houston Memorial 921 Gessner Rd, Houston TX, 77024</td>
<td>Protocol DP 10017 Site 802 115 subjects</td>
<td>April 10 to 13 and April 24, 25, and 30, 2018</td>
<td>VAI pending</td>
</tr>
<tr>
<td>CI: Sergio Bergese, M.D. The Ohio State University Wexner Medical Center, N-411 Doan Hall, 410 W. 10th Avenue, Columbus, Ohio, 43210</td>
<td>Protocol DP 10019 Site 952 83 subjects</td>
<td>March 26 to 30, 2018</td>
<td>VAI</td>
</tr>
</tbody>
</table>

**Compliance Classifications**

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.
1. Prof Dr. Peter Kranke  
   University Hospitals of Würzburg, Department of Anaesthesia and Critical Care  
   Oberdürrbacher Str. 6, 97080, Würzburg, Germany  

For Protocol DP10018 at this site, 302 subjects were screened, 102 subjects were enrolled, and 101 subjects completed the study. For Protocol DP10019 at this site, 361 subjects were screened, 78 subjects were enrolled and completed the study. Review of 100% of all subject records was conducted for informed consent process, staff training, and test article accountability. Review of 30% of all subject records was conducted for efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence, data verification, and test article accountably records were compared to line listings from the NDA. No significant deviations or discrepancies were noted and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The studies appear to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. Ngai Liu, MD., Ph.D.  
   Hopital FOCH, 40 rue Worth, Paris, France  

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

For Protocol DP 10017 at this site, 69 subjects were screened, 61 enrolled, and 60 subjects completed the study. Records for 40 subjects were reviewed comprehensively and compared to line listings from the NDA. All 40 subject records were reviewed for informed consent, drug accountability, and verification for efficacy data. All source documents were available with times of scores of nausea/vomiting and rescue medications given were recorded and matched data listings provided. Concomitant medications and follow up phone calls were also documented with no discrepancies. Protocol deviations were recorded appropriately and there was no apparent un-blinding for this study.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.
3. David Leiman, M.D.
Christus St. John Hospital, Nassau Bay, TX 77058

Note: Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

At this site, for Protocol DP 10015, a total of 59 subjects were screened, 55 subjects enrolled in the study, and 53 subjects completed the study. A total of 21 subject records were reviewed. The data in the line listings was compared with the source documents. No significant deviations or discrepancies were noted and no Form 483 was issued. There was no evidence of under reporting of adverse events. There were minor deviations to the protocol such as out of window visits and missing laboratory values. The deviations were documented and submitted to the IRB.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

4. Harold Minkowitz, M.D.
Houston Memorial, Houston TX, 77024

Note: Observations below for this CI inspection are based on review of the Form FDA 483 and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

At this site, for Protocol DP 10019, a total of 115 subjects were enrolled and 106 completed the study. A total of 21 subject records were reviewed. The data in the line listings was compared with the source documents. There was no evidence of under reporting of adverse events and all efficacy endpoint data was verifiable.

A Form FDA 483 was issued because of the observation that the investigation was not conducted in accordance with the signed statement of the investigator and the investigational plan. Specifically:

1. Ten of the 21 subjects reviewed by the FDA investigator had major protocol violations because the subjects received improper combination prophylactic antiemetic therapy before or during surgery or combination treatment for emesis after surgery. Of these ten subjects, six were randomized to test article (Subjects (b) (6)) and four were randomized to placebo (Subjects (b) (6)).

2. Training of the sub investigators was not documented by the investigator.

Reviewer note: The violations above appear to have occurred equally in the test article and placebo group and were reported in the line listings.
The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

5. Sergio Bergese, M.D.
The Ohio State University, Wexner Medical Center, Columbus, Ohio, 43210

At this site, for Protocol DP 10019, a total of 222 subjects were screened, 83 subjects enrolled and completed the study. A total of 41 subject records were reviewed. The data in the line listings was compared with the source documents. There was no evidence of under reporting of adverse events and all efficacy endpoint data was verifiable.

A Form FDA 483 was issued for the following two observations:
1. Unused supplies of an investigational drug were not returned to the sponsor and disposed of in accordance with sponsor instructions. Specifically, the investigator did not account for the final disposition of two unused investigational drug supply kits.
2. An investigation was not conducted in accordance with the signed statement of the investigator. Specifically:
   a. Section 6.4 of the protocol states that the investigator is responsible for ensuring that dosing is administered in compliance with the protocol and delegation of the task must be clearly documented and approved by the Investigator. Site Signature Log-Delegation of duties document that Sub-Investigators (Sub-Is), S.M., M.E., D.R., B.R., and W.A oversaw dosing and administration of the investigational product between the dates of [redacted] for a total of 15 out of the 41 subjects reviewed during this inspection. The Investigator delegation approval signature for these Sub-I’s in the site Signature Log-Delegation of duties is dated [redacted].
   b. Section 7.3.1 of the protocol states, “any Serious Adverse Event (SAE) occurring during the study period irrespective of the treatment received by the subject must be reported to the sponsor within 24 hours.” Subject [redacted] received study drug on [redacted] and suffered an SAE of non-ST elevated myocardial infection on [redacted]. Site source records document that the SAE was reported to the sponsor on May 9, 2016

Reviewer comment: The above items, although protocol violations, do not impact the efficacy or safety data collected at the site.

The CI responded adequately in a letter dated April 12, 2018 to the violations cited on the Form FDA 483. The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.
6. Acacia Pharma  
   Cambridge CB22 7GG, United Kingdom

Note: Observations below for this sponsor inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocols DP10015, DP10017, DP10018, and DP10019, including selection and oversight of contract research organizations (CROs), monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring for the clinical sites above, and handling of adverse events and other sponsor/monitor related activities. A total of 30% of the site files were reviewed to assess monitoring across the four studies. Sites were adequately monitored and no site was observed to reach a level of noncompliance where intervention was necessary. Routine monitoring through a contracted vendor kept investigators up to date on improvement areas. No violations were noted and no Form FDA 483 was issued.

The studies appear to have been conducted adequately and the data generated by this sponsor may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.  
Team Leader  
Covering for Kassa Ayalew, Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations
cc:
Central Doc. Rm.
Review Division /Division Director/Dragos Roman
Review Division /Medical Team Leader/Anil Rajpal
Review Division /Project Manager/Mimi Phan
Review Division/Medical Officer/Marjorie Dannis
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN LEIBENHAUT
06/07/2018

SUSAN D THOMPSON
06/07/2018
Division of Pediatric and Maternal Health Review

Date: May 15, 2018  Date consulted: November 15, 2017

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health
Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Error Products (DGIEP)

NDA: 209510

Drug: TRADENAME (amisulpride) solution for injection for intravenous use

Applicant: Acacia Pharma Ltd.

Subject: Pregnancy and Lactation Labeling

Proposed Indications:
- Prevention of post-operative nausea and vomiting (PONV), either alone or in combination with other antiemetics,
- Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis

Materials Reviewed:
- 11/15/2017, DPMH consult form, NDA 209510, DARRTS Reference ID 4181367
- 8/2/2017, New Drug Application submission, NDA 209510, amisulpride solution for injection
Consult Question: “DGIEP requests DPMH Pediatric and Maternal Health team’s assistance with the review of this application and its label (PI)”

INTRODUCTION
The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of amisulpride solution for injection labeling.

REGULATORY HISTORY
On August 2, 2017, Acacia Pharma Ltd., submitted New Drug Application 209510 for APD421 (amisulpride) solution for injection for the management of postoperative nausea and vomiting (PONV). Amisulpride is currently approved in more than 50 countries worldwide as an oral agent for treatment of acute and chronic psychotic disorders and has been reformulated as a solution for intravenous (IV) infusion for this proposed NDA.

BACKGROUND
Drug Characteristics
- Amisulpride is a selective antagonist of Dopamine (D2 and D3 receptors
- Amisulpride is excreted 75% in the urine and 25% in the feces and undergoes little or no hepatic metabolism
- The elimination half-life is 0.7 to 8 hours
- The volume of distribution in body tissues is > 100 L and plasma protein binding is 17-30%

Post-operative nausea and vomiting (PONV) and Pregnancy
Approximately 30% of patients suffer from nausea and vomiting in the postanesthetic (24 hour) period after surgery. Nausea and vomiting can complicate recovery due to risk of dehydration, esophageal rupture, pneumothorax and increased intracranial pressure. Treatment can be complicated as nausea and vomiting can be triggered by a multitude of mechanisms. The four main drug classes used for PONV are anticholinergics, antihistamines, D2 antagonists and 5HT3 antagonists.1 There are no guidelines on post-operative nausea and vomiting during pregnancy.

REVIEW
PREGNANCY
Nonclinical Experience
In animal reproduction studies in rats and rabbits, no adverse developmental effects were observed with oral amisulpride during organogenesis at 43 and 645 times the highest recommended human dose, respectively. The reader is referred to the Pharmacology/Toxicology review by Dinesh Guatam, Ph.D.

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Review of Literature
The applicant’s search of published literature did not reveal any data on the exposure of amisulpride during pregnancy. Likewise, DPMH conducted a search of published literature using PubMed and Embase regarding amisulpride exposure during pregnancy using the following search terms, “amisulpride and fetal malformations,” “amisulpride and spontaneous abortion and miscarriage,” “amisulpride and embryofetotoxicity.” Only one case report was located.

Uguz (2016), contains one case report of amisulpride exposure during pregnancy. A 35-year-old pregnant female with schizophrenia diagnosed 15 years prior received aripiprazole 15 mg/day through gestational month five, amisulpride 400 mg/day through entire pregnancy with the exception of a month-long break at gestational month five. Haloperidol 5 mg/day was also added at gestational month six when amisulpride was restarted. No information on infant’s birth was provided. The infant’s pediatrician reported that there was nothing negative to report on the infant up to 12 months of age. The female subject continued the same drug regimen postpartum, and the authors stated that extrapyramidal symptoms were not observed in the infant. No additional information was given.

According to Micromedex, “No data are available on the safe use of amisulpride in pregnant women. Neonates exposed to amisulpride during the third trimester of pregnancy are at increased risk of extrapyramidal and withdrawal symptoms at birth, and neonatal agitation, hypertonia, hypotonia, tremors, somnolence, respiratory distress, and feeding disorders have been reported. Animal reproductive toxicity studies indicated no teratogenic effects occurred, but decreased fertility was noted due to elevated plasma prolactin levels.”

Reviewer comment: DPMH notes that the citation above from Micromedex is a summary from the amisulpride oral tablet non-US label. Amisulpride is approved in other countries including Europe in tablet form for schizophrenia in doses from 50 to 1200 mg/day. DPMH does not recommend this language for the amisulpride US labeling as the proposed indication is different and given in a single dose of 5 mg (prevention of PONV) to 10mg (treatment of PONV) infused intravenously over 1 to 2 minutes at the time of induction of anesthesia; whereas, the indication outside of the US is for schizophrenia and given daily in doses from 50 to 1200 mg, which is both 10-100 times higher and intended to be used chronically. In addition, there were no extrapyramidal symptoms observed in the adults treated with intravenous amisulpride (5 or 10mg) during clinical trials.

Review of Pharmacovigilance Database
One pregnancy was documented in the APD421 treated groups during the clinical development program. No adverse fetal outcome was reported. No additional information was given.

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Summary
Overall, there are little data in published literature on amisulpride exposure during pregnancy in the form of one incomplete case report and one reported pregnancy in the clinical development program where no fetal adverse outcomes were reported; therefore, the human data section will be omitted from subsection 8.1 Pregnancy. Additionally, animal reproduction studies do not indicate a risk of teratogenicity.

LACTATION
Nonclinical Experience
There are no available nonclinical data on amisulpride use and lactation.

Review of Literature
Applicant’s Review of Literature
The applicant conducted a review of published literature regarding amisulpride use and lactating women. Three publications were found that report on amisulpride concentrations in the milk of lactating women exposed to oral amisulpride.

Ilett et al. (2010),4 describe a case report of a 35-year-old female with a history of treatment resistant depression who was breastfeeding her five-month old infant. The patient had been taking amisulpride 100 mg twice daily for approximately 13-weeks and desvenlafaxine 250 mg once daily for 14-weeks prior to the collection of breastmilk samples. According to the authors, pediatric clinical assessment showed an infant who was growing appropriately (weight and length at 50th percentile and head circumference at 75th percentile) and developing normally (Denver Developmental age matching chronological age). An absolute infant dose was calculated based on the average concentration in milk and assumed milk intake of 0.15 L/kg/day (183 mg/kg/day for amisulpride). The relative infant dose was an estimation of absolute infant dose expressed as a percentage of the maternal dose in µg/kg/day. The relative infant dose for amisulpride was 6.1%, and the milk:plasma ratio was 10.7. See table 1 below from publication.

Table 1. Milk and plasma concentrations (Ilett et al. 2010,4 page 706 of publication)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Desvenlafaxine</th>
<th>Amisulpride</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-24h (µg.h/L)</td>
<td>47,000</td>
<td>29,318</td>
</tr>
<tr>
<td>Cavg (µg/L)</td>
<td>1958</td>
<td>1222</td>
</tr>
<tr>
<td>Absolute infant dose (µg/kg/d)</td>
<td>294</td>
<td>183</td>
</tr>
<tr>
<td>Relative infant dose (%)*</td>
<td>7.8</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Plasma

<table>
<thead>
<tr>
<th></th>
<th>Maternal (µg/L)</th>
<th>Infant (µg/L)</th>
<th>Infant exposure (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>780</td>
<td>13</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*As percent of the maternal weight-adjusted doses which were 3782 µg/kg/d for desvenlafaxine and 3026 µg/kg/d for amisulpride.
†Concentration in infant plasma as percent of that in maternal plasma.

4 Ilett K et al., 2010, Assessment of Infant Dose Through Milk in a Lactating Woman Taking Amisulpride and Desvenlafaxine for Treatment-Resistance Depression, Ther Drug Monit, 32:702-707.
A case report presented by Teoh et al., 2011,\(^5\) describes a 28-year-old female patient with bipolar disorder and schizophrenia who was breastfeeding a 13-month-old infant. The patient was taking olanzapine throughout pregnancy and was switched to amisulpride (400 mg/day) 13 months postnatally. Eight samples of milk and one maternal blood sample were taken in a 24-hour period nine days after switching to amisulpride therapy. A milk/plasma ratio was calculated at 19.5 (5,188 µg/L in milk and 266 µg/L in plasma). The absolute infant dose was 534 µg/kg/day, which was calculated by using the average amisulpride concentration in milk 3562 µg/L multiplied by an average milk intake of 0.15L/kg/day. The relative infant dose was 10.7% of maternal weight-adjusted dose (5000 µg/kg/day). The infant was evaluated by a neonatal pediatrician and was reported to be “in good health with an appropriate Denver development score for her age” and did not demonstrate any drug-related adverse events. The authors recommended that the patient stop breastfeeding given the high transfer of amisulpride into milk and based on the infant’s age; the authors felt that the infant already benefited largely from being breastfed.

In a case report by O’Halloran et al. 2016,\(^6\) amisulpride levels were measured in breastmilk from a 32-year-old female breastfeeding exclusively four days after the birth of a healthy newborn at 38-weeks gestation. The patient had been taking 100 mg twice daily of amisulpride beginning at 34 weeks’ gestation due to psychosis and anxiety. The patient was also taking acetaminophen, a multivitamin and occasionally lorazepam. Breastmilk samples were taken pre-dose and four subsequent times in a 12-hour period. A blood sample was collected from the mother and infant at approximately three hours after the amisulpride dose. The authors noted that an infant taking 0.15 L/Kg/day of breast milk would ingest an amisulpride dose of 0.134 mg/kg/day or 4.7% of the maternal weight-adjusted dose. The authors calculated a milk/plasma ratio of 11.9 and noted that amisulpride levels in breastmilk were 12-times higher than the plasma concentration. The infant’s amisulpride plasma concentration was 10.5% of the maternal plasma concentration. See table 2 below of the authors’ comparison with other two discussed publications. The authors noted that there was no evidence of acute toxicity observed in the infant immediately after collection of the plasma specimen.

| Table 2. Publication Comparison (O’Halloran et al. 2016,\(^6\) page 497) |
|-----------------|-----------------|-----------------|
|                 | Current Case    | Teoh et al., 2011 | Hett et al., 2010 |
| Baby age        | 4 d             | 13 mo           | 5 mo             |
| Maternal daily dose, mg | 200              | 400             | 200              |
| Milk AUC_{0-12}, mcg·h·L^{-1} | 10.726         | 84,883          | 14,659           |
| Milk C_{mean}, mcg/L | 894             | 3562            | 1222             |
| Milk/plasma ratio | 11.9            | 19.5            | 10.7             |
| Absolute infant dose, mg·kg^{-1}·d^{-1} | 134             | 534             | 183              |
| Relative infant dose, % | 4.7             | 10.7            | 6.1              |
| Infant exposure, % | 19.5            | NA              | 3.9              |

\(^5\) Teoh et al., 2011, Estimation of rac-Amisulpride Transfer into Milk and of Infant Dose via Milk During Its Use in a Lactating Woman with Bipolar Disorder and Schizophrenia, Breastfeeding Medicine, 6(2):85-88.
Applicant’s Clinical Trial
A single dose of intravenous amisulpride caused a reversible rise in serum prolactin level, from a mean of 9 ng/mL at baseline to 27 ng/mL after treatment (upper limit of normal 29 ng/mL in nonpregnant females, 18 ng/mL in males), which returned to baseline levels within 24 hours and was not associated with any clinical consequences.

DPMH’s Review of Literature
DPMH conducted a review of available published literature on the use of amisulpride during lactation using Embase, PubMed, LactMed and Medication and Mothers’ Milk. No data were found in Medication and Mothers’ Milk. DPMH located one additional article by Uguz (2016), which describes a case report of a 35-year-old female with schizophrenia who took amisulpride 400 mg/day and haloperidol 5 mg/day while breastfeeding for 12 months. According to the authors, the mother did not report any negative effects from the treatment on the infant. The infant was subsequently followed up to 15 months of age with no adverse outcomes reported. No further information was given.

LactMed summarizes the same published literature summarized in the section above. Also, according to LactMed, “Because there is little published experience with amisulpride during breastfeeding and excretion into breastmilk is higher than with other pharmacologically similar drugs, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.”

Additionally, it is well documented that dopamine D2 receptor antagonists increase serum prolactin levels. Hyperprolactinemia can lead to hypogonadism causing infertility, oligomenorrhea, or amenorrhea and less frequently galactorrhea. Prolactin levels typically range from 4 to 15.2 ng/mL in adult males and 4.8-23.3ng/mL in adult females and certain medications such as D2 receptor antagonists can raise levels up to 200 ng/mL. Mild hyperprolactinemia is considered when levels are between 20 to 50 ng/mL, moderate 50 to 100 ng/mL and over 100 ng/mL is associated with hypogonadism. Also, serum prolactin levels naturally increase during pregnancy peaking at delivery. There are numerous publications documenting the increase in serum prolactin levels with amisulpride use; however, it appears to

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8 http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
be reversible after cessation of drug. In one study by Paparrigopoulos (2007), amisulpride was taken by 17 patients with psychiatric disorders at doses ranging from 50 to 800 mg/day along with other medications. Plasma prolactin was 26.7 ± 9.4 days (range: 13 to 50 days). Higher levels of prolactin were observed in females than males and all levels decreased significantly after discontinuation of drug (mean±S.D.prolactin levels: 12.3±6.7 ng/ml). The authors found no correlation between prolactin levels and amisulpride dosage or duration of administration. This increase in serum prolactin levels was also observed in the amisulpride clinical trials. There was an increase in serum prolactin documented after a single IV 5 mg dose from a mean of 9 ng/mL (baseline) to 27 ng/mL after treatment in nonpregnant females and 18 ng/mL in males which returned to baseline within 24 hours after dose. According to LactMed, “the prolactin level in a mother with established lactation may not affect her ability to breastfeed.”

Summary
Although there is no information regarding intravenous amisulpride use and lactation, there are four publications that report on oral maternal use of amisulpride and lactation. Three case reports quantify the levels of amisulpride in the milk of lactating mothers, and one report describes the use of oral amisulpride during breastfeeding for 12 months with no adverse reactions reported in the breastfeeding infant. Among the three available publications, the relative infant dose of amisulpride has been reported to range between 4.7 to 10.7% of the maternal weight-adjusted dosage with milk/plasma (M/P) ratios ranging between 10.7 and 19.5. There are no reports of adverse effects noted in any of the breastfed infants who were exposed to amisulpride. In addition, there are available data on the increase in serum prolactin levels after oral amisulpride exposure that appears to be reversible after discontinuation.

Since the four publications report on breastfeeding women taking high doses of amisulpride (200mg to 400mg daily) and given the lack of significant adverse effects seen in adults treated with low doses of amisulpride and the lack of adverse events seen in breastfed infants treated with high dose amisulpride, DPMH recommends that the following risk/benefit statement is included under subsection 8.2, Lactation:

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.

However, due to the high M/P ratio (If the M/P ratio is <1, then it is usually safe to breastfeed), noted with oral amisulpride, DPMH recommends adding the following Clinical Consideration:

14 Paparrigopoulos T et al., 2007, Amisulpride-induced hyperprolactinemia is reversible following discontinuation, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 31:92-96.
15 Ruzic K et al., 2011, Hyperprolactinaemia with Amisulpride, Psychiatria Danaubina, 23(1):92-94.
17 8/2/2017, New Drug Application submission, NDA 209510, amisulpride solution for injection
A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 48 hours after TRADENAME administration in order to minimize drug exposure to a breastfed infant.

**FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

Nonclinical Experience

The effects of amisulpride on fertility was studied in rats at oral doses up to 160 mg/kg/day. (with exposures up to 43-times the human exposure at the maximum recommended dose). Most female animals (90-95%) at each dose level remained in diestrus and failed to mate. However, this effect on mating reversed following cessation of treatment. No treatment-related effects were observed on uterine/implantation parameters or sperm counts, sperm motility or sperm morphology. The reader is referred to the Pharmacology/Toxicology review by Dinesh Guatam, Ph.D.

Review of Literature

The applicant conducted a review of published literature with regard to amisulpride and females and males of reproductive potential. Likewise, DPMH conducted a search of published literature using PubMed and Embase and no data were found. As discussed in the Lactation section above, D₂ antagonists, such as amisulpride, can increase serum prolactin levels. Hyperprolactinemia can lead to hypogonadism causing infertility, oligomenorrhea, or amenorrhea and less frequently galactorrhea.

Summary

Although there is documentation of reversible hyperprolactinemia in patients exposed to amisulpride, there are no reports of documented infertility. In animal studies in rats, diestrus and failure to mate was demonstrated when amisulpride was given over a period of 10 days at doses up to 43- times the human exposure at the maximum recommended dose. These effects were reversible upon cessation of drug and no treatment related effects were observed on uterine/implantation parameters or sperm counts, sperm motility or sperm morphology. DPMH will include a summary of the animal fertility study in subsection 8.3 Females and Males of Reproductive Potential under the subheading, Infertility. However, since the drug will be given at low doses and for a short duration, no language regarding effects of amisulpride on human fertility are warranted.

**CONCLUSIONS**

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of TRADENAME labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The “Pregnancy” subsection of labeling was formatted in the PLLR format to include: “Risk Summary,” and “Data” subheadings.

- **Lactation, Section 8.2**
  - The “Lactation” subsection of labeling was formatted in the PLLR format to include: the “Risk Summary,” and “Clinical Considerations,” subheadings.
- **Females and Males of Reproductive Potential, Section 8.3**
  - The “Females and Males of Reproductive Potential” subsection of labeling was formatted in the PLLR format to include: “Infertility” subheading.

- **Patient Counseling Information, Section 17**
  - The “Patient Counseling Information” section of labeling was updated to correspond with changes made to section 8.2 of labeling.

**LABELING RECOMMENDATIONS**
DPMH revised sections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

**DPMH Proposed Pregnancy and Lactation Labeling**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

------------USE IN SPECIFIC POPULATIONS------------

- **Lactation**: A lactating woman may pump and discard breast milk for 48 hours after TRADENAME administration. (8.2)

**FULL PRESCRIBING INFORMATION**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Available data with amisulpride use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, there were no adverse developmental effects observed with oral administration of amisulpride in rats and rabbits during the period of organogenesis at exposures about 43 and 645 times, respectively, the exposure delivered by the highest recommended human dose (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

**Animal Data**
Reproduction studies of amisulpride were conducted in pregnant rats administered oral doses up to 160 mg/kg per day (43 times the exposure on area under the curve (AUC) at the highest recommended dose of 10 mg) throughout the period of organogenesis. No adverse embryo-fetal developmental effects were observed at any dose level. Maternal animals exhibited a dose-related decrease in overall mean body weight gain. In rabbits administered amisulpride throughout the period of organogenesis, oral doses up to 210 mg/kg/day (645 times the exposure based on AUC) the highest recommended dose of 10 mg) had no adverse developmental effects on the fetus. Maternal animals exhibited reduced mean body weight gain at doses of 100 and 210 mg/kg/day and reduced food intake was observed at 210 mg/kg/day.
The pre- and post-natal developmental effects of amisulpride were assessed in rats administered oral doses of 60, 100 or 160 mg/kg/day during the periods of organogenesis and lactation. At 160 mg/kg/day (43 times the exposure based on AUC at the highest recommended dose of 10 mg), maternal animals exhibited a reduction in mean body weight gain and decrease in food intake during lactation. Amisulpride had no effect on maternal pregnancy parameters, litter survival or pup growth, development or maturation at any dose tested.

8.2 Lactation
Risk Summary
Based on case reports in published literature, amisulpride is present in human milk at concentrations that are 11 to 20-fold higher than human plasma in patients taking multiple oral doses of amisulpride (200 to 400 mg/day). The estimated infant daily dose ranged from 5% to 11% of the maternal dose. There are ways to minimize drug exposure to a breastfed infant (see Clinical Considerations). There are no reports of adverse effects on the breastfed child and no information on the effects of amisulpride on milk production. The pharmacological action of amisulpride, a dopamine-2 (D2) receptor antagonist, may result in an increase in serum prolactin levels, which may lead to a reversible increase in maternal milk production [see Adverse Reactions (6.1)]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.

Clinical Considerations
A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 48 hours after TRADENAME administration to minimize drug exposure to a breastfed infant.

8.3 Females and Males of Reproductive Potential
Infertility
In animal fertility studies, administration of repeated doses of amisulpride over a 10-day period to female rats resulted in infertility that was reversible [see Nonclinical Toxicology (13.1)].

17 PATIENT COUNSELING INFORMATION
Lactation
Women may also consider reducing infant exposure through pumping and discarding breastmilk for 48 hours after TRADENAME administration [see Use in Specific Populations (8.2)].
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARRIE M CERESA
05/15/2018

MIRIAM C DINATALE
05/15/2018

LYNNE P YAO
05/18/2018
Date: May 10, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Mimi Phan, RPM
DGIEP

Subject: QT-IRT Consult to NDA 209510

Note: Any text in the review with a light background should be inferred as copied from the sponsor’s document.

This memo serves as a correction to a previous review that we placed in DARRTS on 01/12/2018. The previous review contains a transcription error in the predicted QTc effect in the “Clinical Pharmacology” assessment, which resulted in an error in the proposed label. The proposed language in section 12.2 should instead read (addition, deletion):

and positive-controlled, crossover (“thorough QT”) study in 40 healthy, Caucasian and Japanese subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 5.0 (7.1) ms after a 2-minute intravenous infusion of 5 mg and 23.4 (25.5) ms after an 8-minute intravenous infusion of 40 mg

A significant exposure response relationship was identified between amisulpride concentration and ΔΔQTcF. Using this exposure-response relationship, 10 mg infused intravenously over has a maximal predicted (95% upper confidence interval) ΔΔQTcF of .

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARS JOHANNESEN
05/10/2018

CHRISTINE E GARNETT
05/10/2018
**LABEL AND LABELING REVIEW**
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public ***

Date of This Review: March 6, 2018
Requesting Office or Division: Division of Gastrointestinal and Inborn Errors Products (DGIEP)
Application Type and Number: NDA 209510
Product Name and Strength: amisulpride injection
5 mg/2 mL (2.5 mg/mL)
Total Product Strength: 5 mg/2 mL
Product Type: Single ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Acacia Pharma
Submission Dates: October 5, 2017
January 30, 2018
OSE RCM #: 2017-1555
DMEPA Primary Reviewer: Sherly Abraham, R.Ph.
DMEPA Team Leader: Sarah K. Vee, Pharm.D.
1 REASON FOR REVIEW

This review evaluates the labels and labeling for amisulpride injection (NDA 209510), 505(b)(2) NDA, submitted on August 3, 2017 and October 5, 2017. On January 30, 2018, revised prescribing information (PI) was submitted. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed PI, container label, and carton labeling for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B-N/A</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C-N/A</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D-N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Acacia Pharma submitted a new 505(b)(2) NDA for amisulpride injection for prevention of post-operative nausea and vomiting (PONV) and treatment of [PONV. Oral formulation of amisulpride is approved in more than 50 countries worldwide for over 30 years for psychotic disorders. The Applicant is seeking first time approval in the US for the amisulpride injection for intravenous infusion.

We identified areas in the PI, container label, and carton labeling that can be improved to increase the clarity of information to promote the safe use of the product. We
confirmed with Office of Pharmaceutical Quality (OPQ) the correct term for this product is single dose. We provide letter-ready recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container label, and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. We provide our recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. FULL PRESCRIBING INFORMATION: Section 2.2 Preparation and Administration

1. We recommend clarifying the storage time of the diluted solution with the Applicant. This section currently states: (b)(4).

2. We also recommend separating and bulleting the dilution instructions to increase the clarity of information presented in the paragraph as shown below:

- Dilution of is not required before administration.
- within 12 hours of removal of the vial from the protective carton.
- administration, inspect the solution for particulate matter and discoloration; discard if.

4.2 RECOMMENDATIONS FOR ACACIA PHARMA

We recommend the following be implemented prior to approval of this NDA:

A. All Container Label and Carton Labeling:

1. Consider revising the statement to “For intravenous infusion only”. We recommend this to minimize the risk of.

2. Revise the container package term to ‘single-dose vial’.
B. Container Label Only:

3. Decrease the prominence of the statement “Rx Only” as this information appears more prominent than the concentration statement. This will avoid crowding and allow more room for other important information on the principal display panel.\(^a\)

4. Add the name of the manufacturer as required by 21 CFR 201.10(i).

C. 10 Vial Package Label Only:

5. Add the “Rx only” statement as this statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for amisulpride that Acacia Pharma submitted on October 5, 2017.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for amisulpride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
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<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
</tbody>
</table>
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,\(^b\) along with postmarket medication error data, we reviewed the amisulpride labels and labeling submitted by Acacia Pharma on October 5, 2017 and January 30, 2018.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

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/s/

SHERLY ABRAHAM
03/06/2018

SARAH K VEE
03/06/2018
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 8, 2019
Requesting Office or Division: Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number: NDA 209510
Product Name and Strength: Barhemsys (amisulpride) injection
Total Product Strength: 5 mg/2 mL (2.5 mg/mL)
Submission date: November 5, 2018
Applicant/Sponsor Name: Acacia Pharma
OSE RCM #: 2017-1555-2
DMEPA Primary Reviewer: Sherly Abraham, R.Ph.
DMEPA Team Leader: Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO
Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. This NDA is a resubmission after resolving the facility inspection deficiencies. We reviewed the labeling in the previous review cycle\(^a\)\(^b\) and our recommendations were implemented. There are no proposed changes to container label and carton labeling except a minor revision to the NDC number on the ten-vial carton labeling.


\(^b\)Abraham, S. Label and Labeling Review for Barhemsys Memo (NDA 209510). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Oct 2. RCM No.: 2018-1555-1
2 CONCLUSION
We find the container label and carton labeling acceptable from medication error perspective and have no further recommendations at this time.

Appendix A: Label and Labeling Submitted on November 5, 2018

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page
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/s/

SHERLY ABRAHAM
02/08/2019 10:26:07 AM

SARAH K VEE
02/08/2019 10:32:28 AM
# Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<table>
<thead>
<tr>
<th>IND or NDA</th>
<th>NDA 209510</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name</strong></td>
<td>Baremsis</td>
</tr>
<tr>
<td><strong>Generic Name</strong></td>
<td>Amisulpride (APD421)</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>Acacia Pharma Ltd.</td>
</tr>
</tbody>
</table>
| **Indication**    | - Prevention of post-operative nausea and vomiting (PONV), either alone or in combination with other antiemetics  
|                   | - Treatment of PONV in patients who have received antiemetic prophylaxis with agent of a different class or no prior prophylaxis |
| **Dosage Form**   | Intravenous dosing |
| **Drug Class**    | D₂ and D₃ receptor antagonist |
| **Therapeutic Dosing Regimen** | Prevention of PONV: 5 mg over 1 to 2 min  
|                   | Treatment of PONV: 10 mg over 4 min (b) (4) |
| **Duration of Therapeutic Use** | Acute |
| **Maximum Tolerated Dose** | Unknown, highest reported single IV dose is 100 mg. |
| **Submission Number and Date** | SDN 001; 03 Aug 2017 |
| **Review Division** | DGIEP |

Note: Any text in the review with a light background should be inferred as copied from the sponsor’s document.

## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

Amisulpride prolonged the QTc interval in a concentration-dependent manner. At a supratherapeutic dose (40 mg infused over 8 min), the maximum mean increase is 24.8 ms [upper bound: 27.2 ms]) and at a lower dose of 5 mg IV over 2 min, the maximum mean increase is 5.2 ms [7.6 ms]. Based on the concentration-QTc analysis, QTc prolongation is expected (9.8 ms [12.6 ms]) at the maximum recommended dose (10 mg over 4 min). Because of the expectation of QTc prolongation at the highest approved dose, which is like that of ondansetron, we are recommending similar labeling language to ondansetron.

The sponsor conducted a 4-way cross-over study to evaluate the effects of amisulpride on the QTc interval. The study included 40 healthy subjects that were randomized to receive amisulpride 5 mg over 2 min, amisulpride 40 mg over 8 min, placebo, and a single oral dose of moxifloxacin 400 mg. The overall summary of findings is presented in Table 1.
and shows an absence of QTc prolongation at the 5 mg dose and significant QTc prolongation at the supratherapeutic dose. In addition, the largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 1, indicating that assay sensitivity was established.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for amisulpride (5 mg and 40 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (hour)</th>
<th>ΔΔQTcF (ms)</th>
<th>90% CI (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride 5 mg over 2 min</td>
<td>0.133</td>
<td>5.2</td>
<td>(2.8, 7.6)</td>
</tr>
<tr>
<td>Amisulpride 40 mg over 8 min</td>
<td>0.133</td>
<td>24.8</td>
<td>(22.4, 27.2)</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg*</td>
<td>4</td>
<td>13.8</td>
<td>(11.5, 16.1)</td>
</tr>
</tbody>
</table>

* Multiple endpoint adjustment of was not applied. The largest lower bound after Bonferroni adjustment for 3 time points was 10.8 ms. This table, central tendency, and categorical analyses were based on data from averaged Day -1 baseline. Using time-matched baseline will not change the interpretation of study results.

The supratherapeutic dose of amisulpride evaluated in this study results in a $C_{\text{max}}$ that is 3.8-times higher than the $C_{\text{max}}$ expected for the highest recommended therapeutic dose (10 mg over 4 min, section 4.2.8.4.1). This exposure is expected to cover the worst case $C_{\text{max}}$ scenario (renal impairment) as amisulpride is administered as a single IV dose.

Because the study did not include the highest proposed therapeutic dose, the sponsor utilized concentration-QTc analysis to project the QTc effect at the highest proposed therapeutic dose. As we have previously informed the sponsor, we agree with this approach if the model describes the data, however, based on our analysis of the data a linear model (as used by the sponsor) is not appropriate. We therefore considered alternative non-linear models and concluded that an emax model was appropriate to describe the observed concentration-QTc relationship for amisulpride. A similar conclusion was made in the “Population PK” report that was submitted by the sponsor. Based on the emax model, we project a ΔΔQTcF of 9.8 ms (12.6 ms) at the highest recommended therapeutic dose.

1.2 Responses to Questions Posed by Review Division

Question: For amisulpride, it would be helpful to know which of the various sections of labeling (i.e. box warning, contraindication or warning and precautions) are recommended, given the results of the QT study and the intended use of the drug.

QT-IRT’s response: We anticipate ~10 ms QTc prolongation at the highest proposed dose in the label and because amisulpride is administered as a single IV dose we do not anticipate a further increase in the $C_{\text{max}}$ for patients with reduced renal function (worst case exposure scenario). The magnitude of QTc prolongation observed for amisulpride is comparable to what was observed for ondansetron and like ondansetron there are post-marketing cases of torsade for amisulpride. Because of the similarity to ondansetron, we are proposing to use the ondansetron as a model for the amisulpride label. Please see section 2 for all our proposed changes to the label.

Reference ID: 4206344
2 PROPOSED LABEL

Please note, that all labeling edits are suggestions only and we defer the final labeling to the review division.

Below are the proposed edits to the label proposed by the sponsor by section (gray heading). For each edit we are including the original proposal by the sponsor (top) followed by our proposed edits below (addition, deletion) and rational for our edits are included to the right.

<table>
<thead>
<tr>
<th>5.1 QT Prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor:</strong></td>
</tr>
<tr>
<td>causes dose-dependent prolongation of the QT interval [see Clinical Pharmacology (12.2)].</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>QT-IRT’s proposed edits:</strong></td>
</tr>
<tr>
<td>causes dose-dependent prolongation of the QT interval [see Clinical Pharmacology (12.2)]. Avoid use of in patients with congenital long QT syndrome.</td>
</tr>
<tr>
<td>ECG monitoring is recommended in the following circumstances: congenital long QT syndrome or other pre-existing arrhythmias/cardiac conduction disorders; electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia); congestive heart failure or patients taking other products that lead to QT prolongation.</td>
</tr>
<tr>
<td>We propose not including . In addition, the magnitude of QTc prolongation is similar to what was observed for ondansetron, and we are therefore proposing similar labeling language for the two products.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. DRUG INTERACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor:</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>QT-IRT’s proposed edits:</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>We are proposing to describe the concerns with co-administration in section 5.1, similar to the ondansetron label.</td>
</tr>
</tbody>
</table>
12.2 Pharmacodynamics

**Sponsor:**

in 40 healthy, Caucasian and Japanese subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 5.0 (7.1) ms after a 2-minute intravenous infusion of 5 mg and 23.4 (25.5) ms after an 8-minute intravenous infusion of 40 mg. A significant exposure-response relationship was identified between amisulpride concentration and ΔΔQTcF. Using this exposure-response relationship, 10 mg infused intravenously over has a maximal predicted (95% upper prediction interval) ΔΔQTcF of 7.99 (9.112.6) ms.

**QT-IRT’s proposed edits:**

We do not agree with the use of a linear model to describe the relationship between amisulpride concentration and the QTc interval. Based on our analysis, an emax model is more appropriate to describe the concentration-QTc relationship. A similar conclusion was reached in the “Population PK” report submitted by the sponsor.

3 BACKGROUND

3.1 PRODUCT INFORMATION

APD421 is an intravenous (IV) formulation of amisulpride for use in the management of post-operative nausea and vomiting (PONV).

Amisulpride is an “atypical antipsychotic”, first approved more than 30 years ago in Europe and now licensed in more than 50 countries worldwide, although not in the USA, as a treatment for acute and chronic schizophrenic disorders, primarily administered as an oral tablet or solution but also available for intramuscular injection.
The primary pharmacology of amisulpride is dopamine D<sub>2</sub> and D<sub>3</sub> receptor antagonism. D<sub>2</sub> receptor antagonists are well established as anti-emetics. D<sub>3</sub> receptors may also play a role in emesis.

3.2 PRECLINICAL INFORMATION

Amisulpride was observed to inhibit the hERG potassium channel in *in vitro* patch clamp experiments with an IC<sub>50</sub> of 44 to 68 μM.

*Reviewer’s Comment:* The results of *in vitro* assessment of hERG, using a protocol that differs from what is currently considered under CiPA, suggest a low potential for inhibition of the hERG potassium channel (IC<sub>50</sub>: ~44 to 68 μM compared to the free clinical C<sub>max</sub> of ~1 nM). Despite the suggestion of a low potential for inhibition of hERG, a concentration dependent prolongation of the QTc interval was observed clinically for amisulpride (section 5.3). Additionally, the relationship between amisulpride concentration and changes in the QTc interval was non-linear, which deviates from our experience with drugs that prolong the QTc interval via inhibition of the hERG potassium channel. Taken altogether, there is a potential that the QTc prolongation observed for amisulpride might be due to inhibition of other cardiac ionic currents, however, this does not impact our proposed labeling recommendations.

3.3 PREVIOUS CLINICAL EXPERIENCE

Limited ECGs were collected in the development program of amisulpride as noted by the sponsor in the pre-NDA meeting minutes: “The sponsor responded that only limited ECG collection was implemented in phase 3.” (DARRTs 04/27/2017). The clinical summary is therefore based on literature reports and FAERS analysis, based on a summary included by the sponsor ([link]).

**Literature**

Several publications report an association of large amisulpride overdoses with QT prolongation and TdP. Isbister et al (Isbister et al, 2006) presented four cases of deliberate self-poisoning (amisulpride doses ranged from 4.6 g to 32 g). In all four cases, the absolute QT prolongation was over 500 ms and three cases it was close to 600 ms. TdP was confirmed by ECG in two cases and a cardiac arrest resulting in death was reported in another. Amisulpride was associated with a rate-dependent bundle branch block in two cases. In a prospective observational study (Isbister et al, 2010) of 83 events of amisulpride overdose in 81 patients (median dose 6 g), serial ECG recordings showed the occurrence of an abnormal QT-heart rate (HR) pair in 61 cases (73%). Bradycardia occurred in 20 cases (24%) and hypotension in 19 (23%). TdP developed in six cases (7%) ingesting doses of 4 g, 4.6 g, 18 g, 24 g, 32 g and 80 g of amisulpride (coingested drugs in two cases). The patient taking 32 g died after a cardiac arrest. Transient rate-dependent bundle-branch block occurred in three cases. Bradycardia, hypokalemia, and hypocalcemia were significantly associated with QT prolongation and TdP. The ECGs from 86 amisulpride overdose events in 66 patients were reviewed for abnormal QT intervals and TdP (Joy et al, 2011). A total of eight patients (9.3%) exhibited TdP (dose range 4 g to 80 g).

Ward reported two cases of deliberate self-poisoning with 5 g and 3.6 g of amisulpride whereby the QTc was 557 ms and 625 ms, respectively (Ward 2005). Hypocalcaemia
was noted in both cases, and the QT prolongation appeared to respond to IV calcium gluconate. Two cases of amisulpride poisoning were described by Tracqui et al, including a fatal case in which the concentration of amisulpride in post-mortem blood was 41.70 g/mL (Tracqui et al, 1995). The other case was a nonfatal overdose (3 g amisulpride) where ECG showed sinus tachycardia and slight QT prolongation (0.38 s) without abnormalities of PQ and QRS segments. Lynch et al presented a fatal case of amisulpride toxicity where the post-mortem blood concentration was 48 mg/L (Lynch et al, 2008). The authors considered the likely mechanism to be ventricular tachyarrhythmias related to drug-induced prolongation of the QT interval.

A systematic review of drug-induced TdP reported in the literature identified one case where amisulpride was the only drug ingested and two cases where patients were taking amisulpride in conjunction with other drugs (Chan et al, 2007). No details of the doses of amisulpride were provided and the authors note that the study did not aim to establish causation for particular drugs and the design was not appropriate for determining the frequency of TdP with each drug.

**FAERS Analyses**

In 2013 Poluzzi and Raschi and co-workers summarized antipsychotic-drug-related voluntary adverse event reporting in the USA (Poluzzi et al, 2013) and Europe (Raschi et al, 2013). They searched specifically for QT prolongation, ventricular tachyarrhythmias and sudden death reported for 37 antipsychotic drugs. A signal for TdP ventricular tachycardia, in the absence of other known torsadogens, was detected for amisulpride (adjusted reporting odds ratio 43.9), cyamemazine (15.5) and olanzapine (7.7) in the USA. Additional cases were identified in Europe, resulting in amisulpride being classified as a “Class A” torsadogen, fulfilling all five criteria they established a priori (Raschi et al, 2013). Though drug dosage was not included in either report, therapeutic drug monitoring studies have reported typical average steady-state plasma levels of amisulpride in the range 300-400 ng/mL (Muller et al, 2007; Bergemann et al, 2004), suggesting that peak plasma levels are likely to be substantially higher and therefore well in excess of the peak levels seen with the intended intravenous doses of 5 mg (approximately 200 ng/mL) and 10 mg (approximately 350 ng/mL) proposed for APD421.

*Reviewer’s Comment: Literature cases of torsade de pointes have been reported for patients taking an overdose of amisulpride (>3 g). Additionally, a review of post-marketing adverse event reports suggests a signal for torsade de pointes for amisulpride. However, based on observed amisulpride steady-state trough concentrations in patients taking amisulpride as an antipsychotic (C_{trough}: 300 to 400 ng/mL), it is anticipated that the C_{max} for the highest proposed dose (10 mg over 4 min) is less than the C_{max} that has been associated with torsade and consistent with the projected QTc change of ~10 ms at this dose.*

### 3.4 Clinical Pharmacology

Appendix 6.1 summarizes the key features of amisulpride’s clinical pharmacology.
4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT has reviewed the protocol for the thorough QT study for amisulpride under IND 114207 on 11/15/2012 and 08/26/2013. The main comments in the last protocol review (dated 08/26/2013) were related to inadequate justification for selection of dose levels and a proposal to inclusion of only two dose levels in the study.

The sponsor submitted the study report DP10013 for APD421, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Double-blind, Four-period Crossover Study to Investigate the Effect of Intravenous APD421 on Cardiac Conduction as Compared to Placebo and Moxifloxacin in Healthy Adult Subjects

4.2.2 Protocol Number

DP10013

4.2.3 Study Dates

22 Nov 2013 to 31 Mar 2014

4.2.4 Objectives

Primary

- To characterize the effects of single intravenous (iv) doses of 5 mg and 40 mg APD421 on the mean QTc interval, from baseline to under treatment values, using the Fridericia correction formula to calculate QTcF.

Secondary

- To describe effect response relationship, specifically the relationship between pharmacokinetics (PK) and QTc interval of APD421 5 mg and 40 mg and QTcF.
- To compare the effects of two dose levels of APD421 (5 mg and 40 mg) with placebo at each assessment time point, on uncorrected QT interval and on QTc interval using the best heart rate correction method chosen under blinded conditions.
- To describe categorical QT/QTc interval data, and qualitative and quantitative electrocardiogram (ECG) variations from baseline.
- To describe and compare the number and the rates of adverse events (AEs) under each treatment.
- To compare moxifloxacin 400 mg (single dose) with placebo on the mean QT/QTc interval, from baseline to under treatment values, using the best heart rate correction method chosen under blinded conditions -
in order to assess the ability of the study to detect differences of clinical significance.

- To describe the PK profiles of APD421 in the study population.

4.2.5 Study Description

4.2.5.1 Design
This is a randomized, 4-sequence, crossover design with four dosing occasions. Each dosing occasion was followed by a washout period of at least 7 days.

4.2.5.2 Controls
The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding
The positive (moxifloxacin) control was not blinded. Other treatment arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms
The treatments were:

- IV-P: iv placebo: 2.5 mL normal saline infused over 2 minutes, and 20 mL normal saline infused over 8 minutes, in parallel syringe drivers starting at the same time.
- T5: single 5 mg iv dose of APD421 infused over 2 minutes.
- T40: single 40 mg iv dose of APD421 infused over 8 minutes.
- M: moxifloxacin, provided as a single, oral 400 mg tablet, preceded by a moxifloxacin placebo, provided as a single, inactive oral tablet.

4.2.6.2 Sponsor’s Justification for Doses
A single iv dose of APD421 (5 mg or 40 mg), moxifloxacin (400 mg) or placebo was administered following breakfast (fed state). The APD421 doses selected were the proposed therapeutic dose in the prevention of PONV (5 mg); and a supra-therapeutic dose of 40 mg, which was eight times the proposed dose in PONV and twice the proposed dose for prevention of acute phase CINV (20 mg). This range allowed extrapolation of the effect of the 20 mg dose. A supra-therapeutic dose that was only twice the proposed highest therapeutic dose was considered justified because of the very low risk of overdose with APD421, as the proposed presentation is a single iv vial containing no more than 20 mg, to be administered in hospital, under medical supervision.

Reviewer’s Comment: Acceptable. The drug is administered IV as a single dose and the highest dose (40 mg over 8 min) covers the highest recommended dose (10 mg over 4 min).

4.2.6.3 Instructions with Regard to Meals
Not applicable, IV formulation.
4.2.6.4 ECG and PK Assessments

Time-matched ECG and PK samples were collected at the following time-points:

- Day 1: predose and 2 min (end of infusion for low dose), 8 min (end of infusion for high dose), 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 12 h and 24 h post-dose

In addition, time-matched ECGs were collected on day -1.

Reviewer’s Comment: Acceptable, the timing of ECG/PK collection are adequate to cover the time of maximum concentration (end of infusion) and allow for detection of delayed effects.

4.2.6.5 Baseline

The establishment of a baseline has two purposes: (1) individuals have specific, spontaneous circadian rhythms that lead to a changing length of their normal physiological QTc interval at different times during a day. It was necessary to define this diurnal variation so that any changes in QTc observed on the “on-drug” study days could be corrected against this (“off-drug”) baseline; (2) subtracting data from a baseline can reduce the variability of the signal; working with the change from baseline instead of raw values increased the precision of the study results and provided narrower confidence intervals. Therefore the baseline which minimised the variability of the signal was chosen; i.e., the one with the smallest standard deviation.

The primary baseline corrections were calculated using averaged QTc baseline values (the mean of all median readings recorded for each time point on the baseline Day -1). This single value (QTcbaselineAV) was used to calculate ΔQTc for each study period.

Time-matched values (median QTc interval of each time point on Day -1 matched to the corresponding values on Day 1) were used in a secondary analysis of the study.

Reviewer’s Comments: Averaged QTc baseline will be used in FDA’s analyses, which is consistent with sponsor’s primary analysis. Interpretation of study results will not change using time-matched baseline as seen from sponsor’s analyses.

4.2.7 ECG Collection

Novel methods of recording ECGs are always of interest, continuous 12-lead Holter recording has the advantage of providing continuous data acquisition available for retrospective analyses such as safety reviews or beat to beat analysis. On the other hand, they make precise ECG acquisition more difficult, leading to an increased variability due to QT/RR hysteresis, which is unwanted noise [Naseem et al., 2009; Lau et al., 1988]. Thus for this study the chosen ECG acquisition method was conventional bedside ECG recorders under direct manual supervision with simultaneous, continuous 12-lead Holter recording acquired from the same ECG tab position using dual electrodes. The standard ECG was acquired electronically in triplicate for each time point using a MAC1200®/MAC1200ST® ECG recorder with immediate data transfer to a GE Medical MUSE® server for later analysis.
4.2.8 Sponsor’s Results

4.2.8.1 Study Subjects
A total of 40 healthy adult subjects (17 females and 23 males) were randomized to the study and were dosed. Thirty-eight (38) subjects completed the study. Subject (b) was withdrawn from the study due to severe non-compliance to the protocol. Subject (b) voluntarily discontinued the study. All subjects were included in all analysis sets except Subject (b), who was included in the safety set but not the PK or PK/PD sets.

The average age (SD) of the 40 subjects was 28.0 (5.5) years, ranging from 21 years to 45 years. Of the 40 subjects randomized, 23 subjects were Caucasian and 17 were Japanese. The 23 Caucasian subjects were of ethnicity Non-Hispanic.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis
The sponsor used linear mixed effects model with sequence, period, treatment, gender and race as fixed factors and average baseline as covariate at each timepoint. The sponsor’s results for primary analysis are displayed in the following Table 2.

Following iv administration of APD421 5 mg, the ΔΔQTcF profile demonstrated no changes of concern. The maximum ΔΔQTcF from average baseline was an increase of 5.0 ms (90% confidence interval 2.8, 7.1 ms) at 8 minutes post-start of infusion. This was a transient increase: at 30 minutes post-start of infusion the mean difference was 2.1 ms (90% confidence interval: 0.1, 4.2 ms).

In contrast, following administration of APD421 40 mg, ΔΔQTcF was 23.4 ms (90% confidence interval: 21.3, 25.5) at 8 minutes (the end of the infusion). The ΔΔQTcF returned to near baseline levels at 6 h post-start of infusion.
Table 2: Difference to Time-Matched Placebo of Change in QTcF from Average Baseline (Sponsor’s Results)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>APD421 5 mg</td>
<td>00.00</td>
<td>2.0</td>
<td>1.29</td>
<td>-0.1</td>
</tr>
<tr>
<td></td>
<td>00.02</td>
<td>3.6</td>
<td>1.28</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>00.08</td>
<td>5.0</td>
<td>1.29</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>00.30</td>
<td>2.1</td>
<td>1.22</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>01.00</td>
<td>1.7</td>
<td>1.42</td>
<td>-0.6</td>
</tr>
<tr>
<td></td>
<td>01.30</td>
<td>0.9</td>
<td>1.16</td>
<td>-1.0</td>
</tr>
<tr>
<td></td>
<td>02.00</td>
<td>0.7</td>
<td>1.27</td>
<td>-1.3</td>
</tr>
<tr>
<td></td>
<td>03.00</td>
<td>0.0</td>
<td>1.24</td>
<td>-2.1</td>
</tr>
<tr>
<td></td>
<td>04.00</td>
<td>1.5</td>
<td>1.37</td>
<td>-0.8</td>
</tr>
<tr>
<td></td>
<td>06.00</td>
<td>0.2</td>
<td>1.13</td>
<td>-1.7</td>
</tr>
<tr>
<td></td>
<td>12.00</td>
<td>0.7</td>
<td>1.13</td>
<td>-1.2</td>
</tr>
<tr>
<td></td>
<td>24.00</td>
<td>-1.7</td>
<td>1.34</td>
<td>-3.9</td>
</tr>
<tr>
<td>APD421 40 mg</td>
<td>00.00</td>
<td>1.3</td>
<td>1.29</td>
<td>-0.8</td>
</tr>
<tr>
<td></td>
<td>00.02</td>
<td>7.9</td>
<td>1.28</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>00.08</td>
<td>23.4</td>
<td>1.28</td>
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<td></td>
<td>00.30</td>
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</tr>
<tr>
<td></td>
<td>03.00</td>
<td>2.4</td>
<td>1.24</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>04.00</td>
<td>4.8</td>
<td>1.37</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>06.00</td>
<td>1.7</td>
<td>1.13</td>
<td>-0.1</td>
</tr>
<tr>
<td></td>
<td>12.00</td>
<td>2.3</td>
<td>1.12</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>24.00</td>
<td>0.4</td>
<td>1.34</td>
<td>-1.9</td>
</tr>
</tbody>
</table>

Data Source: Table 14.3.5.4.1
SE: standard error. Based on a linear mixed effects model with treatment, sex and race as factors and average baseline as covariate.

Source: CSR, Table 12

Reviewer’s Comments: The sponsor’s primary analysis results were consistent with the reviewer’s analyses using averaged Day -1 baseline. Please see the reviewer’s analysis in section 5.2.
4.2.8.2.2 Assay Sensitivity
The Hochberg procedure was applied to the results of the 2, 3 and 4 h time points of the difference between placebo and the positive control moxifloxacin. Values of QTcF began to increase at 3 h after administration of a single 400 mg moxifloxacin tablet (increase of 5.3 ms with 90% confidence interval of 3.3, 7.4 ms). At 4 h post dose, QTcF had increased by 12.3 ms, with the lower band of the 90% confidence interval at 10.1 ms. The difference between placebo and positive control was statistically significant (p=0.0167), demonstrating the appropriate use of moxifloxacin as a positive control in this study at the time points assessed. Moxifloxacin was administered in the fed state and therefore maximum effect was only reached after the end of the period of interest. The sponsor's results for assay sensitivity analysis are displayed in the following Table 3.

Table 3: Test for Assay Sensitivity (Sponsor’s Results)

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>90% Confidence Interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>02:00</td>
<td>1.1</td>
<td>1.28</td>
<td>-1.0</td>
<td>3.2</td>
</tr>
<tr>
<td>03:00</td>
<td>5.3</td>
<td>1.24</td>
<td>3.3</td>
<td>7.4</td>
</tr>
<tr>
<td>04:00</td>
<td>12.3</td>
<td>1.37</td>
<td>10.1</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Source: CSR, Table 12
Reviewer’s Comments: We agree with the sponsor that assay sensitivity was established for the study. Please see the reviewer’s analysis in section 5.2.

4.2.8.2.3 Categorical Analysis
From the sponsor’s report and categorical analysis tables, no subject had QTcF >480 ms under any of the treatments. For active treatments, no subject had a QTcF value above 450 ms after administration of APD421 5 mg; there were 4 subjects (4/39, 10%) who had QTcF >450 ms after the infusion of APD421 40 mg.

No subject had change from baseline in QTcF (ΔQTcF) > 60 ms under any of the treatments. Five subjects (5/39, 12.8%) had ΔQTcF >30 ms after the infusion of APD421 40 mg. No ΔQTcF >30 ms was observed in other treatments.

4.2.8.3 Safety Analysis
There were no deaths, serious adverse events (SAEs) or significant adverse events (AEs) during the study. There were no AEs that led to subject withdrawal.

4.2.8.4 Clinical Pharmacology
4.2.8.4.1 Pharmacokinetic Analysis
The PK results are presented in Table 4. The Cmax observed in the thorough QT study were 3.9-fold higher following administration of 40 mg over 8 min compared with the
expected $C_{\text{max}}$ (337 ng/mL) following 10 mg over 4 min (the maximum recommended dose).

### Table 4: Pharmacokinetic parameters for amisulpride

<table>
<thead>
<tr>
<th></th>
<th>APD421 5 mg</th>
<th></th>
<th>APD421 40 mg</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=39</td>
<td>Mean (SD)</td>
<td>N=39</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>Linear</td>
<td>Log-transformed</td>
<td>Linear</td>
<td>Log-transformed</td>
</tr>
<tr>
<td>AUC$_{\text{0-24}}$ (ng·h/mL)</td>
<td>154.00 (30.17)</td>
<td>5.02 (0.19)</td>
<td>1374.14 (239.47)</td>
<td>7.21 (0.17)</td>
</tr>
<tr>
<td>AUC$_{\text{0-t}}$ (ng·h/mL)</td>
<td>134.59 (30.17)</td>
<td>4.88 (0.23)</td>
<td>1334.01 (228.36)</td>
<td>7.18 (0.17)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>200.49 (139.16)</td>
<td>5.15 (0.52)</td>
<td>1305.44 (329.35)</td>
<td>7.15 (0.24)</td>
</tr>
<tr>
<td>$t_{\text{max}}$(h)$^a$</td>
<td>0.03 (0.033-0.133)</td>
<td>-</td>
<td>0.13 (0.007-0.183)</td>
<td>-</td>
</tr>
<tr>
<td>$t_{\text{ss}}$(h)</td>
<td>4.05 (0.78)</td>
<td>-</td>
<td>5.04 (0.66)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Data Source: Table 14.2.2.1 and Table 14.2.2.2

$^a$Median (range) presented for $t_{\text{max}}$. 

**Source:** *CSR, Table 24*

#### 4.2.8.4.2 Exposure-Response Analysis

The relationship between amisulpride concentration and $\Delta\Delta QTC_F$ was evaluated using a linear mixed effects model. The sponsor asserts that the choice of a linear model is supported by the absence of hysteresis as well as no indication of a violation of the model assumptions in a QQ-plot of the residuals.

**Reviewer’s Comments:** The reviewer agrees that there is an absence of hysteresis, but disagrees with the appropriateness of the linear model used by the sponsor, see section 5.3 for additional details.

## 5 REVIEWERS’ ASSESSMENT

### 5.1 Evaluation of the QT/RR Correction Method

The sponsor used QTcF for their primary analysis, which is acceptable since no large changes in heart rate were observed, i.e., mean changes $\leq 10$ bpm (section 5.2.2). Therefore, no assessment of the QT/RR correction methodology is necessary.

### 5.2 Statistical Assessments

#### 5.2.1 QTc Analysis

**5.2.1.1 The Primary Analysis for APD421**

The statistical reviewer used mixed model to analyze the $\Delta QTC_F$ and $\Delta\Delta QTC_F$ effect. The model includes treatment, sequence, period, time point, and treatment by time point as fixed effects and subject as a random effect. Day -1 averaged baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.
Table 5: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = T5:
APD421 5 mg IV

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>ΔQTcF (ms) APD421 5 mg IV (N=39)</th>
<th>ΔQTcF (ms) Placebo (N=38)</th>
<th>ΔΔTcF (ms) APD421 5 mg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.7</td>
<td>1.2</td>
<td>1.5 (-0.8, 3.9)</td>
</tr>
<tr>
<td>0.033</td>
<td>1.2</td>
<td>-2.3</td>
<td>3.5 (0.7, 6.3)</td>
</tr>
<tr>
<td>0.133</td>
<td>3.4</td>
<td>-1.8</td>
<td>5.2 (2.8, 7.6)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.3</td>
<td>-1.3</td>
<td>1.6 (-0.5, 3.7)</td>
</tr>
<tr>
<td>1</td>
<td>-0.7</td>
<td>-2.3</td>
<td>1.6 (-0.7, 3.9)</td>
</tr>
<tr>
<td>1.5</td>
<td>-2.3</td>
<td>-3.7</td>
<td>1.4 (-0.8, 3.5)</td>
</tr>
<tr>
<td>2</td>
<td>-3.7</td>
<td>-5.0</td>
<td>1.3 (-0.9, 3.6)</td>
</tr>
<tr>
<td>3</td>
<td>-4.7</td>
<td>-4.9</td>
<td>0.2 (-2.0, 2.3)</td>
</tr>
<tr>
<td>4</td>
<td>-4.6</td>
<td>-6.2</td>
<td>1.6 (-0.7, 3.9)</td>
</tr>
<tr>
<td>6</td>
<td>3.3</td>
<td>2.8</td>
<td>0.5 (-1.5, 2.6)</td>
</tr>
<tr>
<td>12</td>
<td>2.2</td>
<td>1.0</td>
<td>1.2 (-1.0, 3.3)</td>
</tr>
<tr>
<td>24</td>
<td>1.4</td>
<td>3.0</td>
<td>-1.6 (-4.1, 0.8)</td>
</tr>
</tbody>
</table>

Table 6: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = T40:
APD421 40 mg IV

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>ΔQTcF (ms) APD421 5 mg IV (N=39)</th>
<th>ΔQTcF (ms) Placebo (N=38)</th>
<th>ΔΔQTcF (ms) APD421 40 mg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>1.2</td>
<td>0.7 (-1.6, 3.1)</td>
</tr>
<tr>
<td>0.033</td>
<td>7.7</td>
<td>-2.3</td>
<td>10.0 (7.2, 12.8)</td>
</tr>
<tr>
<td>0.133</td>
<td>23.0</td>
<td>-1.8</td>
<td>24.8 (22.4, 27.2)</td>
</tr>
<tr>
<td>0.5</td>
<td>15.7</td>
<td>-1.3</td>
<td>17.0 (14.9, 19.1)</td>
</tr>
<tr>
<td>1</td>
<td>9.6</td>
<td>-2.3</td>
<td>11.8 (9.5, 14.2)</td>
</tr>
<tr>
<td>1.5</td>
<td>3.5</td>
<td>-3.7</td>
<td>7.1 (4.9, 9.3)</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>-5.0</td>
<td>6.2 (3.9, 8.5)</td>
</tr>
<tr>
<td>3</td>
<td>-2.5</td>
<td>-4.9</td>
<td>2.4 (0.3, 4.6)</td>
</tr>
<tr>
<td>4</td>
<td>-0.1</td>
<td>-6.2</td>
<td>6.1 (3.8, 8.4)</td>
</tr>
<tr>
<td>6</td>
<td>4.7</td>
<td>2.8</td>
<td>2.0 (-0.1, 4.0)</td>
</tr>
<tr>
<td>12</td>
<td>3.4</td>
<td>1.0</td>
<td>2.3 (0.2, 4.5)</td>
</tr>
<tr>
<td>24</td>
<td>4.1</td>
<td>3.0</td>
<td>1.1 (-1.4, 3.5)</td>
</tr>
</tbody>
</table>

The largest upper bounds of the 2-sided 90% CI for the mean differences between APD421 5 mg IV and placebo, and between APD421 40 mg IV and placebo were 7.6 ms and 27.2 ms, respectively.

Reference ID: 4206344
The same statistical analyses were performed for ΔQTcF using time-matched baseline, and the results were similar, leading to consistent conclusions. The results from time-matched baseline were not posted here.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data as was used to analyze the QT data. The results are presented in Table 7. The largest unadjusted 90% lower confidence interval was 11.5 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 10.8 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>ΔQTcF (ms) Moxifloxacin 400 mg (N=40)</th>
<th>ΔQTcF (ms) Placebo (N=38)</th>
<th>ΔΔQTcF (ms) Moxifloxacin 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.6</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>0.033</td>
<td>-5.5</td>
<td>-2.3</td>
<td>-3.3 (-6.1, -0.5) (-6.9, 0.4)</td>
</tr>
<tr>
<td>0.133</td>
<td>-2.0</td>
<td>-1.8</td>
<td>-0.2 (-2.6, 2.3) (-3.3, 3.0)</td>
</tr>
<tr>
<td>0.5</td>
<td>-3.2</td>
<td>-1.3</td>
<td>-1.9 (-4.0, 0.2) (-4.7, 0.9)</td>
</tr>
<tr>
<td>1</td>
<td>-2.1</td>
<td>-2.3</td>
<td>0.2 (-2.1, 2.5) (-2.8, 3.2)</td>
</tr>
<tr>
<td>1.5</td>
<td>-0.8</td>
<td>-3.7</td>
<td>2.8 (0.6, 5.0) (-0.0, 5.7)</td>
</tr>
<tr>
<td>2</td>
<td>-2.3</td>
<td>-5.0</td>
<td>2.8 (0.5, 5.0) (-0.2, 5.7)</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
<td>-4.9</td>
<td>6.6 (4.5, 8.8) (3.8, 9.5)</td>
</tr>
<tr>
<td>4</td>
<td>7.6</td>
<td>-6.2</td>
<td>13.8 (11.5, 16.1) (10.8, 16.8)</td>
</tr>
<tr>
<td>6</td>
<td>13.8</td>
<td>2.8</td>
<td>11.1 (9.0, 13.1) (8.3, 13.8)</td>
</tr>
<tr>
<td>12</td>
<td>13.3</td>
<td>1.0</td>
<td>12.2 (10.1, 14.4) (9.4, 15.1)</td>
</tr>
<tr>
<td>24</td>
<td>11.9</td>
<td>3.0</td>
<td>8.9 (6.4, 11.3) (5.6, 12.1)</td>
</tr>
</tbody>
</table>

* Bonferroni method was applied for multiple endpoint evaluation to adjust for 3 time points around moxifloxacin Cₘₐₓ.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

(Note: CIs are all unadjusted for multiplicity, including moxifloxacin group)
5.2.1.4  Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms to 500 ms. No subject had QTcF greater than 500 ms.

Table 8: Categorical Analysis for QTcF

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>QTcF&lt;=450 ms</th>
<th>450&lt;=QTcF&lt;=480 ms</th>
<th>480&lt;=QTcF&lt;=500 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
<td>Obs. #</td>
</tr>
<tr>
<td>Baseline</td>
<td>1704</td>
<td>(95.0%)</td>
<td>1699 (99.7%)</td>
<td>5 (0.3%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>456</td>
<td>(100%)</td>
<td>456 (100%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg</td>
<td>468</td>
<td>(92.3%)</td>
<td>464 (99.1%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>APD421 5 mg IV</td>
<td>468</td>
<td>(100%)</td>
<td>468 (100%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>APD421 40 mg IV</td>
<td>467</td>
<td>(82.1%)</td>
<td>456 (97.6%)</td>
<td>10 (2.1%)</td>
</tr>
</tbody>
</table>

Table 9 lists the categorical analysis results for ΔQTcF. No subject’s change from baseline in QTcF was above 60 ms.
Table 9: Categorical Analysis of ΔQTcF

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>ΔQTcF&lt;=30 ms</th>
<th>30&lt;ΔQTcF&lt;=60 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject #</td>
<td>Obs. #</td>
<td>Subject #</td>
<td>Obs. #</td>
</tr>
<tr>
<td>Placebo</td>
<td>456</td>
<td>(100%)</td>
<td>456</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg</td>
<td>468</td>
<td>(100%)</td>
<td>468</td>
</tr>
<tr>
<td>APD421 5 mg IV</td>
<td>468</td>
<td>(100%)</td>
<td>468</td>
</tr>
<tr>
<td>APD421 40 mg IV</td>
<td>467</td>
<td>(82.1%)</td>
<td>459</td>
</tr>
</tbody>
</table>

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limits of 90% CI for the HR mean differences between APD421 5 mg IV and placebo and APD421 40 mg IV and placebo were 3.7 bpm and 7.7 bpm, respectively.

The outlier analysis results for HR are presented in Table 11.

Table 10: Analysis Results of ΔHR and ΔΔHR

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>APD421 5 mg IV (N=39)</th>
<th>APD421 40 mg IV (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔHR (bpm)</td>
<td>ΔΔHR (bpm)</td>
</tr>
<tr>
<td>0</td>
<td>-4.9</td>
<td>-5.8</td>
</tr>
<tr>
<td>0.033</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>0.133</td>
<td>1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>0.5</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>-0.3</td>
</tr>
<tr>
<td>1.5</td>
<td>1.0</td>
<td>-0.1</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>4</td>
<td>-0.1</td>
<td>-1.4</td>
</tr>
<tr>
<td>6</td>
<td>-0.9</td>
<td>-2.9</td>
</tr>
<tr>
<td>12</td>
<td>-2.0</td>
<td>-2.8</td>
</tr>
<tr>
<td>24</td>
<td>-0.6</td>
<td>-1.5</td>
</tr>
</tbody>
</table>
Table 11: Categorical Analysis for HR

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>HR&lt;=100 bpm</th>
<th>HR&gt;100 bpm</th>
<th>HR&gt;45 bpm</th>
<th>HR&lt;=45 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>(100%)</td>
<td>(0.0%)</td>
<td>(82.5%)</td>
<td>(17.5%)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>(100%)</td>
<td>(0.0%)</td>
<td>(86.8%)</td>
<td>(13.2%)</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin 400 mg</td>
<td>(100%)</td>
<td>(0.0%)</td>
<td>(89.7%)</td>
<td>(10.3%)</td>
<td></td>
</tr>
<tr>
<td>APD421 5 mg IV</td>
<td>(100%)</td>
<td>(0.0%)</td>
<td>(87.2%)</td>
<td>(12.8%)</td>
<td></td>
</tr>
<tr>
<td>APD421 40 mg IV</td>
<td>(97.4%)</td>
<td>(2.6%)</td>
<td>(84.6%)</td>
<td>(15.4%)</td>
<td></td>
</tr>
</tbody>
</table>

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI of the PR mean differences between APD421 5 mg IV and placebo and APD421 40 mg IV and placebo were 7.0 ms and 7.1 ms, respectively.

The outlier analysis results for PR are presented in Table 13.

Table 12: Analysis Results of ΔPR and ΔΔPR

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>ΔPR (ms)</th>
<th>ΔΔPR (ms)</th>
<th>ΔPR (ms)</th>
<th>ΔΔPR (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LSmean</td>
<td>LSmean</td>
<td>LSmean</td>
<td>LSmean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>(90% CI)</td>
<td>Placebo</td>
</tr>
<tr>
<td>0</td>
<td>3.6</td>
<td>3.3</td>
<td>0.3 (-2.4, 3.0)</td>
<td>4.0</td>
</tr>
<tr>
<td>0.033</td>
<td>2.5</td>
<td>-0.4</td>
<td>2.9 (-1.2, 7.0)</td>
<td>2.6</td>
</tr>
<tr>
<td>0.133</td>
<td>1.8</td>
<td>2.2</td>
<td>-0.4 (-3.8, 3.0)</td>
<td>3.4</td>
</tr>
<tr>
<td>0.5</td>
<td>0.7</td>
<td>-0.2</td>
<td>0.9 (-1.4, 3.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>1</td>
<td>-2.7</td>
<td>-1.8</td>
<td>-0.9 (-3.1, 1.3)</td>
<td>-1.8</td>
</tr>
<tr>
<td>1.5</td>
<td>-2.9</td>
<td>-3.6</td>
<td>0.7 (-1.7, 3.2)</td>
<td>-3.6</td>
</tr>
<tr>
<td>2</td>
<td>-3.3</td>
<td>-4.0</td>
<td>0.7 (-1.4, 2.7)</td>
<td>-3.3</td>
</tr>
<tr>
<td>3</td>
<td>-3.8</td>
<td>-4.9</td>
<td>1.1 (-1.1, 3.2)</td>
<td>-4.8</td>
</tr>
<tr>
<td>4</td>
<td>-3.2</td>
<td>-4.9</td>
<td>1.7 (-0.3, 3.7)</td>
<td>-4.2</td>
</tr>
<tr>
<td>6</td>
<td>-1.6</td>
<td>-2.3</td>
<td>0.8 (-1.3, 2.8)</td>
<td>-1.2</td>
</tr>
<tr>
<td>12</td>
<td>-1.2</td>
<td>-1.1</td>
<td>-0.1 (-2.5, 2.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>24</td>
<td>0.6</td>
<td>-0.9</td>
<td>1.6 (-0.5, 3.6)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Table 13: Categorical Analysis for PR

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>PR&lt;=200 ms</th>
<th>PR&gt;200 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subj. #</td>
<td>Obs. #</td>
<td>Subj. #</td>
</tr>
<tr>
<td>Baseline</td>
<td>1698</td>
<td>(92.5%)</td>
<td>1655</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>(2.5%)</td>
<td>43</td>
</tr>
<tr>
<td>Placebo</td>
<td>451</td>
<td>(97.4%)</td>
<td>444</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>(1.6%)</td>
<td>7</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg</td>
<td>468</td>
<td>(94.9%)</td>
<td>459</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>(1.9%)</td>
<td>9</td>
</tr>
<tr>
<td>APD421 5 mg IV</td>
<td>459</td>
<td>(94.9%)</td>
<td>451</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>(1.7%)</td>
<td>8</td>
</tr>
<tr>
<td>APD421 40 mg IV</td>
<td>467</td>
<td>(94.9%)</td>
<td>454</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>(2.8%)</td>
<td>13</td>
</tr>
</tbody>
</table>

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI of the QRS mean differences between APD421 5 mg IV and placebo and APD421 40 mg IV and placebo were 2.2 ms and 3.1 ms, respectively.

The outlier analysis results for QRS are presented in Table 15.

Table 14: Analysis Results of ΔQRS and ΔΔQRS

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>APD421 5 mg IV (N=39)</th>
<th>APD421 40 mg IV (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔQRS (ms)</td>
<td>ΔΔQRS (ms)</td>
</tr>
<tr>
<td>0</td>
<td>0.6</td>
<td>-0.3</td>
</tr>
<tr>
<td>0.033</td>
<td>2.5</td>
<td>-0.4</td>
</tr>
<tr>
<td>0.133</td>
<td>2.9</td>
<td>2.3</td>
</tr>
<tr>
<td>0.5</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>-0.2</td>
</tr>
<tr>
<td>1.5</td>
<td>-0.4</td>
<td>-0.3</td>
</tr>
<tr>
<td>2</td>
<td>-1.2</td>
<td>-0.7</td>
</tr>
<tr>
<td>3</td>
<td>-1.5</td>
<td>-2.1</td>
</tr>
<tr>
<td>4</td>
<td>-1.3</td>
<td>-1.7</td>
</tr>
<tr>
<td>6</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>12</td>
<td>-1.1</td>
<td>-1.0</td>
</tr>
<tr>
<td>24</td>
<td>-0.5</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

Reference ID: 4206344
Table 15: Categorical Analysis for QRS

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total N</th>
<th>QRS&lt;=110 ms</th>
<th>QRS&gt;110 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1704</td>
<td>(b)(6) 87.5%</td>
<td>(b)(6) 12.5%</td>
</tr>
<tr>
<td>Placebo</td>
<td>456</td>
<td>(b)(6) 92.1%</td>
<td>(b)(6) 7.9%</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg</td>
<td>468</td>
<td>(b)(6) 84.6%</td>
<td>(b)(6) 15.4%</td>
</tr>
<tr>
<td>APD421 5 mg IV</td>
<td>468</td>
<td>(b)(6) 89.7%</td>
<td>(b)(6) 10.3%</td>
</tr>
<tr>
<td>APD421 40 mg IV</td>
<td>467</td>
<td>(b)(6) 84.6%</td>
<td>(b)(6) 15.4%</td>
</tr>
</tbody>
</table>

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

A linear mixed effects model was developed by the sponsor to predict the exposure at the maximum recommended dose (10 mg over 4 min), which was not evaluated in this study (section 4.2.8.4.2) and the objective of the clinical pharmacology analysis is to assess the appropriateness of the model developed by the sponsor and estimate the mean ΔΔQTcF (90% upper bound) for the maximum recommended dose.

The evaluation of the appropriateness of the model developed by the sponsor consisted of assessing if the key assumptions of a linear direct model was violated: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔΔQTc and 3) presence of non-linear relationship.

An evaluation of the time-course of amisulpride pharmacokinetics and changes in ΔΔHR and ΔΔQTcF is shown in Figure 2, which shows an absence of significant changes in HR and do not appear to show significant hysteresis.
To further support the absence of hysteresis, a plot comparing the mean amisulpride concentration and \(\Delta\Delta QTcF\) per time-point was constructed by time-point by treatment, which is shown in Figure 3. This plot does not suggest the presence of significant hysteresis, which is consistent with the sponsor’s assessment.
After confirming the absence of significant changes in HR and a delay between amisulpride concentration and changes in $\Delta\Delta QTcF$, the reviewer performed an exploratory assessment of the relationship between amisulpride concentration and $\Delta\Delta QTcF$ to determine if a linear model would be appropriate. The results of this assessment are shown in Figure 4, which suggests that a linear model might not be appropriate.

Figure 4: Evaluation of the relationship between amisulpride concentration and $\Delta\Delta QTcF$. The blue lines represent a linear fit (solid) and a loess fit (dashed)

The sponsor stated in their study report that they considered the linear model to be appropriate based on the evaluation of the QQ plot of the residuals, which did not suggest violations of the assumption of the linear model. The reviewer does not agree with the use of QQ plots to determine the appropriateness of the linear model and the exploratory
analysis presented in Figure 4, suggests that a linear model might not be appropriate. To evaluate this further, the reviewer fitted the same model to the data as the sponsor and constructed a goodness-of-fit plot as well the QQ-plot and a plot of amisulpride concentration vs standardized residuals, which is shown in Figure 5 and further supports that a linear model might not be appropriate.

**Figure 5: Evaluation of the appropriateness of the linear model proposed by the sponsor: goodness-of-fit plot (A), QQ plot (B) and standardized residuals vs amisulpride concentration with a loess regression (C).**

Because the linear model did not describe the data well and a prolongation of the QTc interval was observed, the reviewer evaluated the performance of an emax model and a sigmoidal emax model. For both models, the dependent variable and baseline definition was that of the primary model of the sponsor and random effects were included for each (e.g. e0, ec50 and emax for the emax model) using a diagonal covariance structure. Model comparison was done using AIC as well as visual evaluation using model diagnostic plots (e.g. see Figure 5). Lastly, prediction of mean ΔΔQTcF and corresponding 90% confidence intervals were done using non-parametric case-resampling with replacement (N=1000), using subject ID as the resampling unit.

Based on comparison of AIC and model diagnostic plots the emax model described the data better (AIC\(_{linear}\) = 5423.1 vs AIC\(_{emax}\) = 5357.6). This finding is consistent with the proposal of an emax to describe the concentration-QTc relationship in the “Population PK” report submitted by the sponsor ([link](#)). No additional improvement in fit was observed with the sigmoidal emax model (AIC\(_{sigmoidal\ emax}\) = 5361.1) and the emax model was therefore considered appropriate. Finally, the random effect on ec50 was removed from the model without impacting the AIC or model fit (Figure 6).
In addition to the model diagnostics shown in (Figure 6), a goodness-of-fit plot similar to what was shown for the linear model was also generated (Figure 7). The goodness-of-fit plot also supports the appropriateness of the emax model. Of note, the model estimates at the therapeutic and supratherapeutic dose in the study as well as the concentration for the maximum recommended dose is comparable between the emax model in the sponsor’s “Population PK” report and the model developed by the reviewer (Table 16).

**Figure 6: Final model (Emax model without random effect on EC50) diagnostic plots**

**Figure 7: Goodness-of-fit plot for final model (Emax without random effect on EC50)**
Table 16: Comparison of model predicted $\Delta$QTcF for different models

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Linear model</th>
<th>Sponsor’s emax model</th>
<th>Reviewer’s emax model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>170 ng/mL</td>
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</tr>
<tr>
<td>(Therapeutic dose)</td>
<td>2.9 (3.9 to 4.8)</td>
<td>6.1 (7.0 to 7.9)</td>
<td>5.5 (6.6 to 7.6)</td>
</tr>
<tr>
<td></td>
<td>330 ng/mL</td>
<td></td>
<td></td>
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<tr>
<td>(Highest recommended dose)</td>
<td>6 (7 to 8)</td>
<td>10.3 (11.4 to 12.5)</td>
<td>9.8 (11.3 to 12.6)</td>
</tr>
<tr>
<td></td>
<td>1270 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Supratherapeutic dose)</td>
<td>23.3 (25.2 to 27.1)</td>
<td>20.6 (22.4 to 24.2)</td>
<td>18.9 (21.7 to 24.4)</td>
</tr>
</tbody>
</table>

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments
None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments
Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 Other ECG Intervals
No clinically relevant effects on PR and QRS intervals.
## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

*Source: IND 114207, SDN 14*

| Therapeutic dose | Proposed dose for PONV: 5 mg IV single dose  
Likely dose range to be studied for CINV: 10–40 mg IV single dose, followed by oral dosing in the range 20–80 mg once daily for 3 days. |
<table>
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<tbody>
<tr>
<td>Maximum tolerated dose</td>
<td>Highest reported single IV dose with no significant adverse events is 100 mg (<a href="#">Wetzel et al., 1994</a>). No human MTD or NOAEL reported in the literature. Amisulpride is approved for doses up to 1,200 mg/day PO.</td>
</tr>
</tbody>
</table>
| Principal adverse events | Most common adverse events in datasheet (based on chronic oral administration at approved doses) include:  
- Increase in plasma prolactin levels (reversible after discontinuation of amisulpride) – may result in galactorrhea, amenorrhea or menstrual disorders, gynaecomastia, breast pain or breast enlargement, prolactinoma and erectile dysfunction.  
- Insomnia, anxiety, agitation, orgasmic dysfunction.  
- Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50–300 mg/day.  
- Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent.  
- Somnolence.  
- Hypotension.  
- Constipation, nausea, vomiting, dry mouth.  
- Weight gain. |

| Maximum dose tested and exposures achieved | Single Dose | 50 mg IV  
Mean Cmax: 515.2 (±20.2) ng.mL\(^{-1}\)  
Mean AUC: 1,231 (±44) ng.mL\(^{-1}\).h  
400 mg PO (MHRA, 2010)  
Mean Cmax: 1,391 (±602) ng.mL\(^{-1}\)  
Mean AUC: 8,891 (±2,096) ng.mL\(^{-1}\).h  
200 mg PO for 10 days  
Mean Cmax: 453.4 (±42) ng.mL\(^{-1}\)  
Mean AUC: 3,359 (±198) ng.mL\(^{-1}\).h |
<table>
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<tbody>
<tr>
<td>Range of linear PK</td>
<td>PK is linear across the entire range tested both IV (10–50 mg) and PO (50–1200 mg). Specific study of linearity conducted in 18 healthy volunteers with 50, 100 and 200 mg single dose PO.</td>
<td></td>
</tr>
<tr>
<td>Accumulation at steady</td>
<td>No significant accumulation seen with any multiple-dose</td>
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</tr>
<tr>
<td>state</td>
<td>regimen tested, up to and including 1200 mg/day for 29 days. Steady state reached in 3–4 days.</td>
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</tbody>
</table>
| Metabolites | Very little metabolism occurs (<10%). Principal metabolic pathways:  
• Hydroxylation  
• Oxidation of pyrrolidin ring  
• N-deethylation  
(Canal et al, 2002) |
| Absorption | Absorption Absolute/Relative Bioavailability 48% (±3%) |
| Tmax | Parent: two peaks generally seen, one at around 1 hr and a second, higher at 3–4 hours;  
Metabolites: N/A. |
| Distribution | Vd/F or Vd  
5.8 (± 0.4) L.kg⁻¹ (after 50 mg IV administration)  
324 L (after 15 mg IV administration)  
(Canal et al, 2002) |
| % bound | 14% |
| Elimination | Route  
After IV administration  
• Primary route: urinary – 75%  
• Secondary route: fecal – 20%  
(Canal et al, 2002)  
After oral administration  
• Primary route: fecal – 63.6% (±3.1%)  
• Secondary route: urinary – 35.3% (±3.5%) |
| Terminal t½ | Mean for parent: 7 (±0.4) hours for 50 mg IV; 11.9 (±0.7) hours for 200 mg PO.  
Mean for metabolites: N/A |
| CL/F or CL | 41.6 (±1.6) L.h⁻¹ (after 50 mg IV administration) |
| Intrinsic Factors | Age  
No difference between young and elderly healthy volunteers (Hamon-Vilcot et al, 1998) |
| Sex | No specific data available on sex differences. |
| Race | No specific data available on race differences. |
| Hepatic & Renal Impairment | No data available in hepatic impairment.  
Renal impairment (50 mg IM dose):  
• 30-60 mL.min⁻¹ creatinine clearance:  
Cmax = 680 mg.mL⁻¹; AUC = 2,796 (±440) ng.mL⁻¹.h  
• 10-30 mL.min⁻¹ creatinine clearance:  
Cmax = 771 (±77) mg.mL⁻¹; AUC = 4,272 (±897) ng.mL⁻¹.h  
• cf healthy: Cmax = 483 (±40) mg.mL⁻¹; AUC = 1,290 (±56) ng.mL⁻¹.h |
Hemodialysis: little amisulpride cleared.

<table>
<thead>
<tr>
<th>Extrinsic Factors</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ethanol: no effect on PK parameters. Lorazepam: no effect on PK parameters. Lithium: no effect on PK parameters (Canal et al., 2003). Amisulpride is neither a substrate for nor an inhibitor of CYP450 isozymes.</td>
</tr>
</tbody>
</table>

| Food Effects | Comparison of 100 mg oral dose in fasting vs non-fasting subjects  
|             | High-fat meal: no change in Cmax or AUC.  
|             | High-carbohydrate meal: Cmax reduced vs fasting (93.4 vs 133.7 ng.mL\(^{-1}\)); AUC reduced (880 vs 1579 ng.mL\(^{-1}\).h) |

| Expected High Clinical Exposure Scenario | In clinical practice, IV dosing will be carried out in controlled circumstances (hospital/clinic), so the risk of accidental overdose is low. Based on current trial data, the highest IV dose to be used in the clinic is expected to be 20 mg, as single dose in the acute phase of CINV. However, a 40 mg dose will probably be tested as part of dose-ranging in acute-phase CINV. A supra-therapeutic dose of 80 mg, being twice the upper limit of the proposed dose range for Phase II testing, or four times the likely final dose, represents adequate “worst-case” cover. |

References


MHRA. UKPAR on Amisulpride 50mg, 100mg and 200mg tablets PL 19364/0044-6; Amisulpride 400mg film-coated tablets PL 19364/0047. 2010

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