CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209510Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	209510
PDUFA Goal Date	February 26, 2020
OSE RCM #	2017-2096
Reviewer Name	Yasmeen Abou-Sayed, PharmD
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD, MPH
Review Completion Date	November 8, 2019
Subject	Memorandum to File
Established Name	Amisulpride
Trade Name	Barhemsys
Name of Applicant	Acacia Pharma Ltd.
Therapeutic Class	Dopamine D2 Receptor Antagonist
Formulation(s)	Intravenous Solution (2.5mg/ml)
Dosing Regimen	Single 5 mg dose for PONV prophylaxis; or single 10 mg dose for PONV treatment

1 Introduction

This memorandum by the Division of Risk Management (DRISK) pertains to the New Drug Application (NDA) 209510 submitted on August 26, 2019 by Acacia Pharma Inc (Acacia) and evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Barhemsys (amisulpride) is necessary to ensure the benefits outweigh its risks. Acacia received a Complete Response (CR) on May 2, 2019 due to product quality/facility inspections deficiencies.[1] This was preceded by a CR on October 5, 2018 to the initial October 5, 2017 submission of NDA 209510, due to product quality/facility inspection deficiencies.[2] The NDA was resubmitted with the proposed indications for:

- prevention of post-operative nausea and vomiting (PONV), either alone or in combination with other antiemetics, or
- rescue treatment of (b) (4) PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis.

DRISK completed a review on September 24, 2018 and a memorandum on April 29, 2019 that concluded a REMS was not needed based on the risk-benefit profile at the time of completion of those reviews.[3,4] This application is under review in the Division of Gastroenterology and Inborn Errors Products (DGIEP). The Sponsor did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Barhemsys (amisulpride), a new molecular entity (NME)[a], is a dopamine D2 receptor antagonist, proposed for the management of PONV, specifically:

- prevention of post-operative nausea and vomiting (PONV), either alone or in combination with other antiemetics, or
- rescue treatment of (b) (4) PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis.

Amisuplride is proposed as a 2 milliliter (mL) vial of 2.5 milligram (mg)/mL intravenous drug solution, to be administered as a single dose in a surgical setting.[b] Dosing for each indication is as follows:

- Prevention of PONV: 5 mg as a single intravenous injection infused over 1 to 2 minutes at the time of induction of anesthesia, either alone or in combination with other antiemetics
- Treatment of PONV: 10 mg as a single intravenous injection infused over 1-2 minutes in the event of nausea and/or vomiting after a surgical procedure.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Amisulpride is currently approved as an oral or intramuscular antipsychotic in over 50 countries worldwide for over 30 years, but is not approved for any indication in the United States.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for [Application/Number] relevant to this review:

- 10/5/2017: NDA 209510 submission for treatment of prevention of post-operative nausea and vomiting (PONV), either alone or in combination with other antiemetics, or rescue treatment of (b) (4) PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis, received
- 10/5/2018: CR issued due to product quality/facility inspection deficiencies.
- 11/5/2018: NDA 209510 resubmission in response to 10/5/18 CR received
- 5/2/2019: CR issued due to product quality/facility inspection deficiencies.
- 8/26/2019: NDA 209510 resubmission in response to 5/2/19 CR received

3 Discussion of Need for a REMS

The risk associated with amisulpride is QT prolongation. DRISK evaluated this risk in a review dated September 24, 2018, and a memo dated April 29, 2019, and determined that a REMS was not needed to ensure the benefits of amisulpride outweigh the risks at the time of those reviews. No additional safety information was submitted in this review cycle. Therefore, at the time of this memorandum, the safety profile of amisulpride has not changed.

4 Conclusion and Recommendations

Based on the analysis detailed in the initial REMS review, and the absence of new safety data that changes the benefit-risk profile in the resubmission following the Complete Response letter, we maintain our determination that a REMS is not needed to ensure the benefits of amisulpride outweigh its risks. The risk of QT prolongation with amisulpride is similar to another marketed antiemetic, ondansetron, used in the same setting for the same indications, and will be communicated through labeling. The Division of Gastroenterology and Inborn Errors Products and DRISK agree that this risk can be managed in the peri- and post-operative setting for which its use is intended, and is a risk which is known and already managed with the currently approved PONV therapies. Patients in this setting are under close monitoring by various healthcare providers, including an anesthesiologist, and nursing staff.

Should DGIEP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

5 Appendices

5.1 REFERENCES

[1] Division of Gastroenterology and Inborn Errors Products. Complete Response Letter for Amisulpride, NDA 209510, May 2, 2019.

[2] Division of Gastroenterology and Inborn Errors Products. Complete Response Letter for Amisulpride, NDA 209510, October 5, 2018.

[3] Abou-Sayed, Y. REMS Review for NDA 209510 Amisulpride. September 25, 2018.

[4] Abou-Sayed, Y. REMS Memorandum for NDA 209510 Amisulpride. April 29, 2019.

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

Application Type	NDA
Application Number	209510
PDUFA Goal Date	May 5, 2019
OSE RCM #	2017-2096
Reviewer Name(s)	Yasmeen Abou-Sayed, PharmD
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD, MPH
Review Completion Date	April 29, 2019
Subject	Memorandum to File
Established Name	Amisulpride
Trade Name	Barhemsys
Name of Applicant	Acacia Pharma Ltd.
Therapeutic Class	Dopamine D2 Receptor Antagonist
Formulation(s)	Intravenous Solution (2.5mg/ml)
Dosing Regimen	Single 5 mg dose for PONV prophylaxis; or single 10 mg dose for PONV treatment

1 Introduction

This memorandum by the Division of Risk Management (DRISK) pertains to the New Drug Application (NDA) 209510 submitted on November 5, 2018 by Acacia Pharma Inc (Acacia) and evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Barhemsys (amisulpride) is necessary to ensure the benefits outweigh its risks. Acacia received a Complete Response (CR) letter on October 5, 2018, due to product quality/facility inspection deficiencies.[1] The NDA was resubmitted with the proposed indications for:

- prevention of post-operative nausea and vomiting (PONV), either alone or in combination with other antiemetics, or
- rescue treatment of (b) (4) PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis.

DRISK completed a review on September 24, 2018 and concluded that based on the risk-benefit profile, a REMS was not needed.[2] This application is under review in the Division of Gastroenterology and Inborn Errors Products (DGIEP). The Sponsor did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Barhemsys (amisulpride), a new molecular entity (NME)[a], is a dopamine D2 receptor antagonist, proposed for the management of PONV, specifically:

- prevention of post-operative nausea and vomiting (PONV), either alone or in combination with other antiemetics, or
- rescue treatment of (b) (4) PONV in patients who have received antiemetic prophylaxis with an agent of a different class or no prior prophylaxis.

Amisuplride is proposed as a 2 milliliter (mL) vial of 2.5 milligram (mg)/mL intravenous drug solution, to be administered as a single dose in a surgical setting.[b] Dosing for each indication is as follows:

- Prevention of PONV: 5 mg as a single intravenous injection infused over 1 to 2 minutes at the time of induction of anesthesia, either alone or in combination with other antiemetics
- Treatment of PONV: 10 mg as a single intravenous injection infused over 1-2 minutes in the event of nausea and/or vomiting after a surgical procedure.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Amisulpride is currently approved as an oral or intramuscular antipsychotic in over 50 countries worldwide for over 30 years, but is not approved for any indication in the United States.

2.2 REGULATORY HISTORY

The new drug application for amisulpride, NDA 209510, was submitted November 5, 2018 by Acacia Pharma, Ltd. in response to a Complete Response letter issued on October 5, 2018 for product quality/facility inspection deficiencies.

3 Discussion of Need for a REMS

The risk associated with amisulpride is QT prolongation. DRISK evaluated this risk in a review dated September 24, 2018, and determined that a REMS was not needed to ensure the benefits of amisulpride outweigh the risks. A safety update submitted with this review cycle included pharmacokinetic data gathered in a phase one study, Study DP10022 (National Clinical Trial [NCT] 03583489). This study enrolled 30 patients who received single and repeat dosing of 10 mg of amisulpride.[3] There were no safety signals of any kind identified during the study. Therefore, at the time of this memorandum, the safety profile of amisulpride has not changed.

4 Conclusion and Recommendations

Based on the analysis detailed in the initial REMS review, and the absence of new safety data that changes the benefit-risk profile in the resubmission following the Complete Response letter, we maintain our determination that a REMS is not needed to ensure the benefits of amisulpride outweigh its risks. The risk of QT prolongation with amisulpride is similar to another marketed antiemetic, ondansetron, used in the same setting for the same indications, and will be communicated through labeling. The Division of Gastroenterology and Inborn Errors Products and DRISK agree that this risk can be managed in the peri- and post-operative setting for which its use is intended, and is a risk which is known and already managed with the currently approved PONV therapies. Patients in this setting are under close monitoring by various healthcare providers, including the anesthesiologist, and nursing staff.

Should DGIEP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

5 Appendices

5.1 REFERENCES

[1] Division of Gastroenterology and Inborn Errors Products. Complete Response Letter for Amisulpride, NDA 209510, October 5, 2018.

[2] Abou-Sayed, Y. REMS Review for NDA 209510 Amisulpride. September 25, 2018.

[3] Acacia Pharma Ltd. Integrated Summary of Safety – Safety Update Report for Barhemsys, November 5, 2018.

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/s/

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

Application Type	NDA
Application Number	209510
PDUFA Goal Date	October 5, 2018
OSE RCM #	2017-2096
Reviewer Name(s)	Yasmeen Abou-Sayed, PharmD
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	September 24, 2018
Subject	Evaluation of Need for a REMS
Established Name	Amisulpride
Trade Name	Baremsis
Name of Applicant	Acacia Pharma Ltd.
Therapeutic Class	Dopamine D2 receptor antagonist
Formulation(s)	Intravenous solution
Dosing Regimen	5 mg dose for PONV prophylaxis; or a 10 mg dose to treat an episode of PONV

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Barhemsys (amisulpride) is necessary to ensure the benefits outweigh its risks. Acacia Pharma Ltd. (Acacia) submitted a New Drug Application (NDA) 209510 for amisulpride with the proposed indication for the management of post-operative nausea and vomiting (PONV), specifically:

- Prevention of PONV, either alone or in combination with other anti-emetics; and
- Treatment of (b) (4) PONV in patients who have received prior anti-emetic prophylaxis with an agent of a different class or no prior prophylaxis

The risk associated with amisulpride is QT prolongation. The applicant did not submit a proposed REMS or risk management plan with this application. DRISK and the Division of Gastroenterology and Inborn Errors Products (DGIEP) agree that a REMS is not necessary to ensure the benefits of amisuplride outweigh its risks. QT prolongation is a risk that is known and managed in the peri- and post-operative setting, and can be mitigated via labeling and appropriate monitoring.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Barhemsys (amisulpride) is necessary to ensure the benefits outweigh its risks. Acacia submitted a New Drug Application (NDA) 209510 for amisulpride with the proposed indication for the management of post-operative nausea and vomiting (PONV), specifically:

- Prevention of PONV, either alone or in combination with other anti-emetics; and
- Treatment of (b) (4) PONV in patients who have received prior anti-emetic prophylaxis with an agent of a different class or no prior prophylaxis.

This application is under review in the Division of Gastroenterology and Inborn Errors Products (DGIEP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Barhemsys (amisulpride), a new molecular entity (NME)[a], is a dopamine D2 receptor antagonist, proposed for the management of PONV, specifically:

- Prevention of PONV, either alone or in combination with other anti-emetics; and

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

- Treatment of (b) (4) PONV in patients who have received prior anti-emetic prophylaxis with an agent of a different class or no prior prophylaxis.

Amisuplride is proposed as a 2 milliliter (mL) vial of 2.5 milligram (mg)/mL intravenous drug solution, to be administered as a single dose in a surgical setting.[b] Dosing for each indication is as follows:

- Prevention of PONV: 5 mg as a single intravenous injection infused over 1 to 2 minutes at the time of induction of anesthesia, 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: 10 mg as a single intravenous injection infused over 1-2 minutes in the event of nausea and/or vomiting after a surgical procedure

Amisulpride is currently approved as an oral or intramuscular antipsychotic in over 50 countries worldwide for over 30 years, but is not approved for any indication in the United States.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209510 relevant to this review:

- **October 5, 2017**: NDA 209510 submission for prevention of PONV, either alone or in combination with other anti-emetics; and treatment o (b) (4) PONV in patients who have received prior anti-emetic prophylaxis with an agent of a different class or no prior prophylaxis received.
- **March 19, 2018**: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for amisulpride, but that a final determination would be made by the end of the review cycle.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

The term PONV is used to describe nausea and/or vomiting or retching in the post-anesthesia care unit (PACU) and in the immediate 24 hours post-op. Nausea, vomiting, and retching can complicate recovery from anesthesia and patients often rate PONV as worse than postoperative pain.[1] PONV usually resolves on its own, or is treated without further complications, but may require unanticipated hospital admission and delay recovery room discharge.[2] Additionally, vomiting or retching can result in wound

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

rupture, esophageal rupture, aspiration, dehydration, increased intracranial pressure, and pneumothorax. [c]

Five principle neurotransmitter receptors mediate nausea and vomiting: muscarinic M1, dopamine D2, histamine H1 5-hydroxytryptamine, (HT)-3 serotonin, and neurokinin 1 (NK1) – substance P.[3] Any one of these receptors could be targeted for management of PONV; amisulpride's mechanism of action is via dopamine D2 receptor antagonism.

Prevention of PONV in adults is determined by patient risk using 4 principal risk factors:[4]

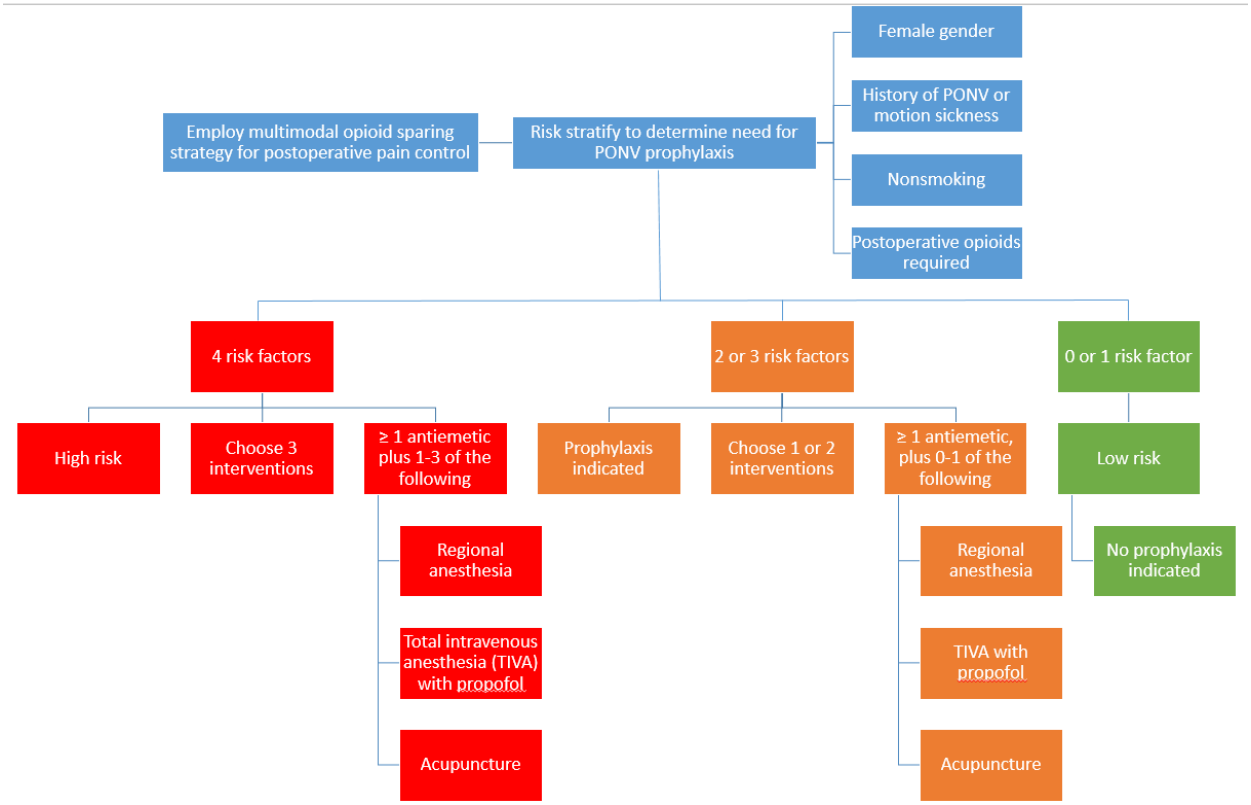
- Female sex
- Being a non-smoker
- Prior history of PONV and/or motion sickness
- Use of opioid analgesics for post-operative pain management

Patients without risk factors may not receive prophylaxis, while those with one risk factor may receive a single anti-emetic. Those with two or more risk factors generally receive combination pharmacotherapy. Despite routine prophylaxis for PONV, PONV still occurs in about 30% of surgical patients.d,5 Patients who experience PONV despite receiving prophylaxis are treated with an anti-emetic drug of a different class from any used in prophylaxis. Table 1 summarrizes the process for determining appropriate management of PONV in a patient.

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1 – Prophylaxis for postoperative nausea and vomiting (PONV) in adults*



*When more than 1 antiemetic is administered, drugs from different classes should be chosen

3.2 Description of Current Treatment Options

Currently, several classes of drugs are used in the management of PONV, including 5-HT3 antagonists, corticosteroids, D2 antagonists, anticholinergics and antihistamines. Appendix 10.1 lists FDA-approved treatment options for PONV. The most commonly used drug for PONV prophylaxis is the 5-HT3-antagonist ondansetron. It is well tolerated, but can cause QT prolongation at doses above those generally used in PONV, and should be used with caution in patients with congenital long QT syndrome. The second most commonly used therapy is the corticosteroid dexamethasone. This is also well tolerated, but may cause issues in patients with diabetes and depression. No single drug or class of drug is completely effective in controlling PONV and therefore combination pharmacotherapy is commonly used, particularly in patients with multiple PONV risk factors. Many of the existing agents have issues related to safety or efficacy which limit their use, such as QT prolongation, unwanted sedation, and extrapyramidal effects. There is, therefore, an unmet medical need for safe and effective new agents that can be used in combination regimens for PONV prophylaxis.

4 Benefit Assessment

The Applicant submitted a total of five Phase 3, randomized, double-blind, placebo-controlled studies to support the use of amisulpride for the management of PONV. Based on the statistical reviewer's

assessment, Study DP10014 (National Clinical Trial [NCT] 01991821), which focused on the prevention of PONV, did not demonstrate superiority of amisulpride to placebo, and therefore will not be included for evaluation in this review. The four remaining pivotal studies for amisulpride are two prophylaxis of PONV Studies (DP10015 [NCT 01991860] and DP10017 [NCT 02337062]) and two treatment of PONV Studies (DP10018 [NCT 02449291] and DP10019 [NCT 02646566]). All four trials were randomized, double-blind, placebo-controlled, multi-center studies assessing the efficacy and safety of amisulpride in patients undergoing elective surgery under general anesthesia. The primary efficacy endpoint studied in all four trials was the incidence of Complete Response (CR), the absence of PONV, defined as no episodes of vomiting or retching and no use of anti-emetic medication, during the first 24 hours after completion of surgery. All secondary endpoints were planned to be exploratory in nature, therefore the results of the secondary endpoints will not be considered by the review team for this application.

4.1 PREVENTION OF PONV

Study DP10015 enrolled adult patients at moderate to high risk of PONV, to compare 5 mg of amisulpride (n=176) versus placebo (n=166). CR occurred in 78 patients on amisulpride (44.3%) and 54 patients (32.5%) on placebo. The difference in rates of CR between amisulpride and placebo was 11.8%, which was statistically significant in favor of amisulpride.

Study DP10017 enrolled adult patients at high risk of PONV, to assess the efficacy of amisulpride at 5 mg (n=572) in combination with a standard anti-emetic in the prevention of PONV, versus placebo (n=575). CR occurred in 330 patients (57.6%) in the amisulpride group and 268 patients (46.6%) in the placebo group. The difference in rate of CR between amisulpride and placebo was 10.9%, which was statistically significant in favor of amisulpride ($p<0.001$).

4.2 TREATMENT OF PONV

Study DP10018 enrolled adult surgical patients at low to moderate risk of PONV, with established PONV post-surgery, and who did not receive PONV prophylaxis, to compare the efficacy of 5 mg (n=191) and 10 mg (n=188) amisulpride to placebo (n=181). CR occurred in 60 patients (31.4%) in the amisulpride 5 mg group, 59 patients (31.4%) in the amisulpride 10 mg group and 39 patients (21.5%) in the placebo group. The difference in rate of CR between amisulpride and placebo for the 5 mg dosing group was 9.87% ($p = 0.015$). The difference in the CR rate for the 10 mg dosing group and placebo was 9.84% ($p=0.016$). These results were determined by the clinical reviewer to not be statistically significant.

Study DP10019 also compared the efficacy of 5 mg (n=237) and 10 mg (n=230) amisulpride to placebo (n=235) as treatment for established PONV in moderate to high risk adult surgical patients who had received prior PONV prophylaxis. CR occurred in 80 patients (33.8%) in the 5 mg group, 96 patients (41.7%) in the 10 mg group and 67 patients (28.5%) in the placebo group. The difference in rate of CR for the 10 mg group versus placebo was 13.23% ($p=0.003$), which was determined by the clinical reviewer to be statistically significant. The difference in rate of CR for the 5 mg group versus placebo was 5.24% ($p=0.22$) and was not statistically significant.

Overall, the clinical reviewer has concluded[6,e]:

- based on the collective evidence from studies DP10015 and DP10017 for the indication of prevention of PONV, amisulpride 5mg demonstrated efficacy compared to placebo, and
- based on collective evidence from studies DP10018 and DP10019 for the indication of treatment of PONV, amisulpride 10mg demonstrated efficacy compared to placebo

5 Risk Assessment & Safe-Use Conditions

The safety database for amisulpride includes data from six randomized, double-blind, placebo-controlled, multi-center studies of patients undergoing general anesthesia and elective surgery, four in the prevention of PONV (studies DP10017, DP10015, DP10014 and DP10006 [dose ranging study]) and two in the treatment of established PONV (studies DP10018 and DP0019). In total, 3313 patients were exposed to study medication (placebo or amisulpride), with 1924 patients exposed to amisulpride and 1389 patients receiving placebo. Post-marketing surveillance (PMS) data for orally administered amisulpride, for chronic psychiatric indications, is available from the European Medicines Agency (EMA). All of the most common adverse events (AEs) are what would be expected with a dopamine antagonist, such as extrapyramidal symptoms, tremor, fatigue, and QT prolongation.[6] Since IV amisulpride is proposed as a single dose treatment, it is not likely that many of the reactions which are typically seen with chronic use will occur.

Common adverse reactions which occurred in at least 2% of amisulpride patients, and at a higher rate than placebo, are detailed in Table 2 below.

Table 2 - Common Adverse Events in Adult Patients in Clinical Trials of Amisulpride*

	BARHEMSYS 5 mg N=967	Placebo N=973
Abdominal distension	2%	1%
Procedural hypotension	3%	2%
Hypokalemia	3%	2%
Chills	3%	2%
Blood prolactin increased**	3%	0%

*reported in at least 2% of patients treated with amisulpride and at a higher rate than placebo

**A single dose of amisulpride caused a reversible rise in serum prolactin, 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.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Serious adverse events (SAEs)[f] occurred in 2.8% of placebo patients versus 2.6% of amisulpride treated patients. Table 3 shows the number of SAEs that occurred in the clinical development program. All of these serious adverse events could occur as a complication of surgery, thus could typically be seen in any post-op patient population.[g]

Table 3 – Number of SAEs in the amisulpride clinical development program

SAE	Placebo (n=1389)	Amisulpride 5mg or 10 mg (n=1813)
Post Procedural Hemorrhage	**3**	**3**
Postoperative Ileus	**3**	**3**
Gastrointestinal anastomotic leak	**2**	**0**
Vomiting	**4**	**1**
Small intestinal obstruction	**2**	**2**
Abdominal Pain	**2**	**0**
Peritonitis	**1**	**2**
Postoperative wound infection	**0**	**2**
Acute respiraotory failure	**0**	**2**

5.1 DEATHS

There was one death in the amisulpride clinical development program. The patient was a 65 year old female with a past medical history of diabetes, morbid obesity, and hypertension and was randomized to receive 5 mg of amisulpride and combination anti-emetic (ondansetron) in trial DP10017. She had an open exploratory laparotomy, with a colon resection and extensive lysis of adhesions. During her post-operative course, the patient experienced systemic inflammatory response syndrome (SIRS), acute renal failure requiring dialysis, metabolic acidosis hyperglycemia, and hypocalcemia. Three days after receiving amisulpride, she had ventricular fibrillation and subsequently died. The study investigators

[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

assessed her death as not being related to the amisulpride received three days prior to her death, and the clinical reviewer for the Agency concurs based on her multiple comorbidities, complex open abdominal surgery, and complicated post-operative course.

5.2 QT INTERVAL PROLONGATION

Amisulpride is known to prolong the QT interval in a concentration-dependent manner.[7] Across the Phase 3 trials for amisulpride, 7 patients had QT prolongation (5 in amisulpride, 2 in placebo). Of the 5 events in the amisulpride group, 4 were mild and occurred anywhere from 2 to 29 hours after treatment. These events were noted, but patients received no treatment and no negative outcomes were associated with them. The fifth patient experienced QT prolongation that was classified as moderate and was also an SAE.

In addition to the data collected from the phase 3 trials, a thorough QT (tQT) study (DP10013) was conducted at 5 mg infused over 1-2 min and at a supratherapeutic dose of 40 mg infused over 8 min. 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 showed an absence of QT prolongation at the 5 mg dose and significant QT prolongation at the supratherapeutic dose. The Agency's Interdisciplinary Review Team for QT Studies (IRT-QT) analyzed the results, which are summarized in Table 4.[8]

Table 4 – FDA analysis of QT prolongation results of Study DP10013, with 90% confidence intervals (CI)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Amisulpride 5 mg over 2 min	0.133	5.2	(2.8, 7.6)
Amisulpride 40 mg over 8 min	0.133	24.8	(22.4, 27.2)
Moxifloxacin 400 mg	4	13.8	(11.5, 16.1)

As amisulpride 10 mg was not studied in the tQT study, the QT prolongation at 10 mg was predicted based on the relationship between exposure and change in QT. Based on the IRT-QT's concentration-QT analysis at the highest recommended dose (10 mg infused over 1 min), the largest change in QT is predicted to be 12.6 milliseconds (ms) (90% upper CI: 14.1 ms).

Given that amisulpride prolongs the QT interval concentration-dependently, caution should be exercised when amisulpride is administered concomitantly with other medications known to cause significant QT prolongation. Amisuplride is likely to be used in combination with ondansetron in particular; although QT prolongation is not expected at therapeutic doses of ondansetron, the additive effect with amisulpride is of concern. Given a minimal risk of QT prolongation at amisulpride 5 mg, amisulpride 5 mg for prevention of PONV can be simultaneously administered with ondansetron. However, in order to minimize the risk of QT prolongation which is expected at amisulpride 10 mg, the clinical reviewer is recommending that amisulpride 10 mg and ondansetron should be given at least 30 minutes apart, [redacted] (b) (4). Droperidol is a D2 antagonist like amisulpride, and is indicated for the prevention of PONV. It has been reported to cause significant QT prolongation at recommended doses. Concomitant use would be contraindicated, [redacted] (b) (4)

(b) (4). For patients taking other drugs known to prolong QT interval, close ECG monitoring is recommended. Ongoing label negotiations propose including the risk of QT prolongation in Section 5, Warnings and Precautions, of the Prescribing Information (PI).[9]

6 Expected Postmarket Use

The proposed use of amisulpride is as a single IV administration of a 5 mg dose for PONV prophylaxis, given at the time of induction of anesthesia, or a single IV administration of a 10 mg dose to treat an episode of PONV. Amisulpride would be used in outpatient and inpatient surgical settings, prescribed by surgeons, anesthesiologists, and nurse anesthetists, and administered by the anesthesiologist, anesthethist, or nurse in the post-anesthesia care unit (PACU). The patient in this setting is under close observation during the surgery, with electrocardiographic (ECG) monitoring of the heart rhythm a standard of care during the procedure. Close monitoring is also routine in the post-operative setting, with ECG monitoring warranted for patients who may be at an increased risk of arrhythmias.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for amisulpride beyond routine pharmacovigilance and labeling. The Applicant states that given the routinely close monitoring of peri/post-operative patients, the overall risk to the patient of QT prolongation is minimal, and labeling will adequately mitigate the risks and preserve benefits in the treatment of PONV.

8 Discussion of Need for a REMS

Adequate management of PONV is important to ensure patient recovery and prevent potential complications of surgery. While multiple treatment options are available, amisulpride can offer an additional option for patients whose PONV is not adequately managed by available therapies.

Based on the results from trials DP10015, DP10017, DP10018, and DP10019, amisulpride demonstrated efficacy and safety based on complete response of PONV versus patients treated with placebo. The Division of Gastroenterology and Inborn Errors Products recommends approval of amisulpride on the basis of the efficacy and safety information currently available.

An increased risk of QT prolongation exists with the 10 mg dose of amisulpride for the treatment of PONV. The proposed labeling includes the risk of QT prolongation in the Warnings and Precautions (Section 5), as well as considerations for use with other drugs that prolong the QT interval in the Drug Interactions (Section 7.2). Currently, the proposed label advises that (b) (4)

(b) (4)

(b) (4). Ondansetron is used for the same indication and in the same setting, with a similar risk of QT prolongation, which is currently communicated via labeling. This risk can be

managed in the peri- and post-operative setting for which its use is intended, and is a risk which is known and already managed, since it is a potential risk with currently approved therapies. Patients in this setting are under close monitoring by various healthcare providers, including the anesthesiologist, and nursing staff.

DRISK agrees that the adverse event profile of the drug does not warrant risk mitigation beyond labeling. Based on the currently available data, DRISK and DGIEP concur that a REMS is not necessary to ensure the benefits of amisulpride outweigh the risks.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with amisulpride are well understood in the peri/post-operative setting and healthcare providers who manage surgical patients should be familiar with the risk of QT prolongation from anti-emetics, and the importance of patient monitoring.

Should DGIEP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 Summary of Treatment Options for PONV

Product (Generic) Year of Approval	Indication	Dosing & Administration	Important Safety and Tolerability Issues	Risk Management
FDA Approved Treatments				
Zofran (Ondansetron) *1991*	Prevention of PONV	16 mg orally 1 hour before anesthesia; 4 mg IV immediately prior to anesthesia	QT prolongation in a dose-dependent manner; hypersensitivity; serotonin syndrome	N/A
Aloxi (Palonosetron) *2003*	Prevention and/or Treatment of PONV	0.075 mg IV immediately prior to anesthesia	Hypersensitivity; Serotonin syndrome	N/A
Emend (aprepitant) *2003*	Prevention of PONV	40 mg orally 3 hours prior to anesthesia	CYP3A4 interactions	N/A
Inapsine (droperidol) *1970*	Prevention of PONV	2.5 mg IV and IM	QT prolongation	Boxed Warning
Reglan (metoclopramide) *1980*	Prevention of PONV	10 mg IM near the end of surgery	Tardive dyskinesia	Boxed Warning
Phenergan (promethazine) *1951*	Prevention and/or Treatment of PONV	12.5 to 25 mg every 4 hours as needed - orally, rectally, IV, or IM	Respiratory depression in pediatric patients under age 2	Boxed warning
Transderm Scop (scopolamine) *1979*	Prevention of PONV	Apply 1mg/72 hour patch behind ear evening before surgery	Withdrawal	N/A

Product (Generic) Year of Approval	Indication	Dosing & Administration	Important Safety and Tolerability Issues	Risk Management
Tigan (Trimtho-benzamide HCL) *1974*	Treatment of PONV	200 mg IM 3 – 4 times daily	Hypersensitivity	N/A
Non-FDA Approved Treatments				
Decadron (dexamethasone) *1959*	Steroidal anti-inflammatory	8 mg IV before surgery	Fluid and electrolyte disturbances	N/A
Compazine (prochlorperazine) *1957*	Treatment of severe nausea or vomiting	5-10 mg IM, or 2.5-10 mg IV before OR after surgery, also can be used 25 mg rectally after surgery	Extrapyramidal symptoms	Boxed warning - Increased Mortality in Elderly Patients with Dementia-Related Psychosis
*Anzemet (dolasetron) – was FDA approved for prevention of PONV, a drug safety communication was issued 12/17/10 warning of risk of potentially fatal abnormal heart rhythm (torsades de points) – based on QT prolongation. USA marketing was suspended shortly after, and indication for PONV management was removed from labeling in 2014. w				

10.2 DESCRIPTION OF THE PHASE 3 EFFICACY STUDIES

Trial Identity	Study Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/Follow Up	No. of Subjects	Study Population	No. of Centers And Countries
Controlled Studies to Support Efficacy and Safety							
DP10014	**Prophylaxis** Randomized 1:1, double-blind, multi-center, placebo-controlled, Phase 3	5 mg IV Placebo IV	PONV	from 31 July 2013 to 17 January 2014	**Enrolled** 368 **Treated** 347 (Amisulpride 5mg:169, Placebo: 178)	Females and males age ≥18 at moderate to high risk of PONV and were undergoing elective surgery under general anesthesia, for elective surgery that required overnight admission to hospital, and was scheduled to last at least 1 hour from induction of anesthesia	France (4 sites) and Germany (6 sites)
DP10015	**Prophylaxis** Randomized 1:1, double-blind, multi-center, placebo-controlled, Phase 3	5 mg IV Placebo IV	PONV	between 8 and 22 days from 13 August 2013 to 28 January 2014	**Enrolled** 364 **Treated** 342 (Amisulpride 5mg:176, Placebo: 166)	Females and males age ≥18 at risk of PONV undergoing elective, in-patient surgery using an open or laparoscopic surgical technique, under general anesthesia scheduled to last at least one hour from induction of anesthesia and requiring at least one overnight stay in hospital	USA (9 sites)
DP10017	**Prophylaxis** Randomized 1:1, double-blind, multi-center, placebo-controlled, Phase3b	5 mg IV Placebo IV Both (Given in combination with a standard anti-emetic that was not a dopamine D2 Antagonist)	PONV	from 12 February 2015 to 28 September 2015	**Enrolled** 1297 **Treated** 1204 (Amisulpride 5mg:572, Placebo: 575)	Females and males age ≥18 at risk of PONV undergoing elective, in-patient surgery using an open or laparoscopic surgical technique, under general anesthesia scheduled to last at least one hour from induction of anesthesia and requiring at least one overnight stay in hospital	Germany (7 sites), France (7 sites) and USA (15 sites)
DP10018	**Treatment** Randomized 1:1:1, double-blind, multi-center, placebo-controlled, Phase3	5 mg IV 10 mg IV Placebo IV	PONV	from 09 August 2015 to 18 July 2016	**Enrolled** 1988 **Treated** 560 (Amisulpride 10mg: 188, Amisulpride 5mg: 191, Placebo: 181)	Females and males age ≥18 at low to moderate risk for PONV who were undergoing elective ambulatory (day-case) or in-patient surgery under general inhalational anesthesia and had received no prior PONV prophylaxis	Germany (5 sites), France (2 sites), Canada (3 sites) and USA (10 sites)

Trial Identity	Study Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/Follow Up	No. of Subjects	Study Population	No. of Centers And Countries
DP10019	**Treatment** Randomized 1:1:1, double-blind, multi-center, placebo-controlled, Phase 3	5 mg IV 10 mg IV Placebo IV	PONV	From 20 January 2017 to 31 March 2017	**Enrolled** 2285 **Treated** 702 (Amisulpride 10mg: 230 , Amisulpride 5mg:237 , Placebo:235)	Females and males age ≥18 surgical patients with moderate-to-high risk of PONV who had received prior prophylaxis with an agent of a different class from amisulpride (i.e., not a dopamine antagonist)	Germany (5 sites), France (2 sites), Canada (3 sites) and USA (13 sites)

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