# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214907Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

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| Application Type | NDA |
| Application Number | 214907 |
| PDUFA Goal Date | November 29, 2021 |
| OSE RCM # | 2020-2755 |
| | |
| Reviewer Name(s) | Brad Moriyama, Pharm.D., BCCCP |
| Team Leader | Naomi Boston, Pharm.D. |
| Division Director | Cynthia LaCivita, Pharm.D. |
| Review Completion Date | November 4, 2021 |
| Subject | Evaluation of Need for a REMS |
| | |
| Established Name | pafolacianine |
| Trade Name | Cytalux |
| Name of Applicant | On Target Laboratories, Inc. |
| Therapeutic Class | optical imaging agent |
| Formulation(s) | 3.2 mg vial |
| Dosing Regimen | pafolacianine 0.025 mg/kg intravenous infusion, 1 hour to 9 hours prior to surgery |

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# EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Cytalux (pafolacianine) is necessary to ensure the benefits outweigh its risks. On Target Laboratories, Inc. submitted a New Drug Application (NDA) 214907 for pafolacianine with the proposed indication in adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant lesions. The serious risks associated with pafolacianine include infusion-related reactions, risk of misinterpretation, embryo-fetal toxicity, and risk of pafolacianine aggregation and infusion reactions if the incorrect diluent is used to prepare pafolacianine. The applicant did not submit a proposed REMS or risk management plan.

DRM and the Division of Imaging and Radiation Medicine (DIRM) agree that a REMS is not necessary to ensure the benefits of pafolacianine outweigh its risks. The efficacy of pafolacianine was supported by Study OTL-2016-OTL38-006, in which the pafolacianine group had a detection proportion under fluorescent light but not under normal light or palpation of 26.9%. The serious risks associated with pafolacianine of infusion-related reactions, risk of misinterpretation, embryo-fetal toxicity, and risk of pafolacianine aggregation and infusion reactions will be communicated in the warnings and precautions section of the label.

# 1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Cytalux (pafolacianine) is necessary to ensure the benefits outweigh its risks. On Target Laboratories, Inc. submitted a New Drug Application (NDA) 214907 for pafolacianine with the proposed indication in adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant lesions.[1] This application is under review in the Division of Imaging and Radiation Medicine (DIRM). The applicant did not submit a proposed REMS or risk management plan.

# 2 Background

## 2.1 PRODUCT INFORMATION

Cytalux (pafolacianine), an NME, is an optical imaging agent, proposed in adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant lesions. Pafolacianine is a fluorescent drug that targets folate receptors which may be overexpressed in ovarian cancer. Pafolacianine is supplied as a 3.2 mg vial. The proposed dosing regimen is pafolacianine 0.025 mg/kg single intravenous infusion, 1 hour to 9 hours prior to surgery.[b] Pafolacianine is not currently approved in any jurisdiction. Pafolacianine was designated as an orphan product and received fast track designation.

## 2.2 REGULATORY HISTORY

[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.*

The following is a summary of the regulatory history for pafolacianine NDA 214907 relevant to this review:

- 12/23/2014: Orphan drug designation granted
- 08/11/2016: Fast track designation granted
- 12/29/2020: NDA 214907 submission in adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant lesions received
- 04/23/2021: 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 pafolacianine
- 08/18/2021: Major amendment letter sent to the applicant; PDUFA goal date extended by 3 months due to a major amendment regarding product quality.

# 3 Therapeutic Context and Treatment Options

## 3.1 Description of the Medical Condition

Ovarian cancer is the 5th leading cause of death from cancer in women in the United States.[2,3] The estimated number of new cases and the estimated number of deaths of ovarian cancer in the United States in women is 21,410 and 13,770, respectively.[2,c] The five-year relative survival of localized, regional, and distant ovarian cancer is 92.6%, 74.8%, and 30.3%, respectively.[4,d]

## 3.2 Description of Current Treatment Options

In patients with ovarian cancer primary debulking cytoreductive surgery followed by chemotherapy is standard treatment.[5]

# 4 Benefit Assessment

The pivotal trial NCT 03180307 (Study OTL-2016-OTL38-006) supporting this application for efficacy and safety consisted of a Phase 3, multicenter, open-label, randomized trial which evaluated pafolacianine in women diagnosed with ovarian cancer or with high clinical suspicion of ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery.[1,5] Patients (N=150) received pafolacianine 0.025 mg/kg at least 1 hour before initiation of fluorescence imaging, with 134 patients receiving both normal light imaging evaluation and fluorescence imaging

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

[d] 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.*

evaluation. The primary endpoint was the proportion of patients with at least one evaluable ovarian cancer lesion confirmed by central pathology that was detected with pafolacianine under fluorescent light but not under normal light or palpation and not otherwise identified for resection prior to surgery. The pafolacianine treatment group had a detection proportion under fluorescent light but not under normal light or palpation of 26.9% (95% CI 19.6% to 35.2%). The FDA clinical reviewer concluded that pafolacianine was effective as an adjunct for the intraoperative identification of malignant lesions in patients with ovarian cancer.[e]

# 5 Risk Assessment & Safe-Use Conditions

The safety of pafolacianine was evaluated in studies NCT 03180307 (OTL-2016-OTL38-006), OTL-2014-OTL38-003, and NCT 02872701 (OTL-2016-OTL38-005).[1,5,f] Study OTL-2014-OTL38-003 was a Phase 2 single dose, open-label, multicenter study in patients with ovarian cancer. Study OTL-2016-OTL38-005 was a Phase 2 single dose, open-label study in patients with lung cancer. In the combined safety population from studies OTL-2016-OTL38-006, OTL-2014-OTL38-003, and OTL-2016-OTL38-005, 294 patients received pafolacianine. Common adverse reactions reported with pafolacianine included nausea, vomiting, abdominal pain, flushing, dyspepsia, chest discomfort, pruritus and hypersensitivity.

The serious risks[g] associated with pafolacianine which include infusion-related reactions, risk of misinterpretation, embryo-fetal toxicity, and risk of pafolacianine aggregation and infusion reactions are summarized in the sections below.

## 5.1 INFUSION-RELATED REACTIONS

Section 5.1 of the draft labeling states that adverse reactions including nausea, vomiting, abdominal pain, flushing, dyspepsia, chest discomfort, and pruritus occurred in 2.4% of patients receiving pafolacianine. The proposed label states that treatment with antihistamines and/or anti-nausea medication may be used. Section 5.1 of the draft labeling also states if an adverse reaction occurs during drug administration, the infusion can be interrupted and resumed after treatment of the

[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.*

[f] 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.*

[g] 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.

reaction. If approved, these risks will be communicated in the warnings and precautions section of the label.

### 5.2 Risk of Misinterpretation

Section 5.2 of the draft labeling states that errors may occur with the use of pafolacianine during intraoperative fluorescence imaging to detect ovarian cancer, including false negatives and false positives. Non-fluorescing tissue in the surgical field does not rule out the presence of ovarian cancer and fluorescence may be seen in non-cancerous tissue including areas of the bowel, kidneys, lymph nodes and inflamed tissue. If approved, this risk will be communicated in the warnings and precautions section of the label.

### 5.3 Embryo-Fetal Toxicity

Pafolacianine may cause fetal harm based on the mechanism of action of the drug. No clinical data is available with pafolacianine in pregnancy in humans. The proposed label states to advise females of reproductive potential of the potential risk to a fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting pafolacianine. If approved, this risk will be communicated in the warnings and precautions section of the label.

### 5.4 Risk of Pafolacianine Aggregation and Infusion Reactions

Section 5.4 of the draft labeling states that using the incorrect diluent to prepare the pafolacianine infusion solution can cause the aggregation of pafolacianine and can induce infusion reactions such as nausea, vomiting, abdominal pain, or rash. The proposed label recommends to use only 5% Dextrose Injection to prepare the pafolacianine infusion solution and to not use other diluents. If approved, this risk will be communicated in the warnings and precautions section of the label.

## 6 Expected Postmarket Use

If approved, pafolacianine will primarily be used in inpatient settings. The likely prescribers will be surgeons and oncologist.

## 7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for pafolacianine beyond routine pharmacovigilance and labeling.

## 8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of pafolacianine on the basis of the efficacy and safety information currently available. The efficacy of pafolacianine was supported by Study OTL-2016-OTL38-006, in which the pafolacianine group had a detection proportion under fluorescent light but not under normal light or palpation of 26.9%. The serious risks associated with pafolacianine of infusion-related reactions, risk of misinterpretation, embryo-fetal toxicity, and risk of pafolacianine aggregation and

infusion reactions if the incorrect diluent is used to prepare pafolacianine. These risks will be communicated in the warnings and precautions section of the label. Based on the efficacy and risk associated with pafolacianine in adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant lesions, the DRM and DIRM recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks. The likely prescribers will be surgeons and oncologist who should have experience managing the serious adverse events reported with pafolacianine.

# 9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore a REMS is not necessary for pafolacianine to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

# 10 Appendices

## 10.1 References

[1] Proposed prescribing information for pafolacianine as currently edited by FDA, October 24, 2021.

[2] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33.

[3] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 1.2021 – February 26, 2021). https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf (accessed 2021 August 3).

[4] Cancer Stat Facts: Ovarian Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/ovary.html (accessed 2021 August 3).

[5] Pafolacianine multi-disciplinary review and evaluation. Accessed October 25, 2021.

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