CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214907Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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 13, 2021
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214907
Product Name and Strength:	Cytalux (pafolacianine) Injection, 3.2 mg/1.6 mL (2 mg/mL)
Applicant/Sponsor Name:	On Target Laboratories
OSE RCM #:	2020-2754-3
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

On Target Laboratories submitted revised single vial carton labeling and 10-vial pack carton labeling on October 8, 2021 for Cytalux (pafolacianine) injection under NDA 214907. We reviewed the revised single vial carton labeling and 10-vial pack carton labeling for Cytalux (Appendix A) to determine if they are acceptable from a medication error perspective. We note revisions were made in order to align with the revised information in the Cytalux Prescribing Information (PI) regarding the thawing instructions.

2 CONCLUSION

On Target Laboratories implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

DEVIN R KANE
10/13/2021 01:04:34 PM

HINA S MEHTA
10/13/2021 02:29:34 PM

Consult Memorandum

Date:	06/03/2021
To:	Sharon Thomas, CDER/OND/ORO/DROSM Joseph Rajendran, CDER/OND/OSM/DIRM
From:	Arpita Roy, Scientific Reviewer, MPCB/DMGP/OHT7/CDRH
Through:	Shyam Kalavar, Team Lead, MPCB/DMGP/OHT7/CDRH Soma Ghosh, Branch Chief, MPCB/DMGP/OHT7/CDRH Reena Philip, Director, DMGP/OHT7/CDRH
ICC Number:	ICCR# 00084169; ICC2100438
Protocol Title:	Study OTL-2016-OTL38-006 (Study 006) A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection (OTL38) for Intraoperative Imaging of Folate Receptor Positive Ovarian Cancer
Subject:	Consult request- NDA 214907
Drug Name:	Pafolacianine sodium injection (OTL38)
Drug Sponsor	On Target Laboratories, Inc.
Biomarker(s):	Folate Receptor (FR, alpha and beta isoforms)
Device Sponsor:	Biocare Medical Folate Receptor alpha IHC Assay kit
Related Submissions:	None

I. BACKGROUND and PURPOSE

Expression of FRα occurs frequently, especially in the common high-grade, high-stage serous epithelial ovarian tumors that are most likely to recur. Hence, FR-based diagnostic and therapeutic strategies have been and continue to be used to identify malignant tissue in the treatment of ovarian cancer. On Target Laboratories, Inc. (OTL) has developed pafolacianine sodium injection (OTL38), a folic acid analogue conjugated with an indole cyanine green-like dye as a tumor-specific imaging agent.

The efficacy of pafolacianine sodium injection was confirmed in 1 pivotal study (Phase 3 Study 006) and 1 supporting study (Phase 2 Study 003). For Study 006, the primary efficacy endpoint was the proportion of patients with at least 1 evaluable FR+ ovarian cancer lesion confirmed by central pathology (standard of truth) that was detected using the pafolacianine and fluorescent light but not under normal light or palpation.

II. CDRH RESPONSE TO CDER QUESTIONS:

IHC was performed in addition to histopathology to establish the primary efficacy end point of having at least one ovarian cancer lesion identified using Pafolacianine and NIR light that was not

identified by standard of care normal light or palpation during debulking surgery. OTL used a commercially available IHC kit from Biocare Medical Folate Receptor alpha IHC Assay kit.

CDER requested CDRH to provide comments for the following:

- Regulatory status of IHC tests for FR alpha and beta expression
  - Explain what components of the IHC tests are FDA cleared
- CDRH guidance in assessing/analyzing the FR IHC assay data and acceptability of sponsor responses to CDER comments to the sponsor as follows:
  - Provide the results of your analyses that validate the accuracy of the FR IHC testing as conducted by the central pathology laboratory for the purpose of the truth standard

CDRH comments to CDER:

1. There are no FDA approved or cleared IHC assays to assess the expression of folate alpha or beta receptors.

2. Based on the concerns mentioned below the accuracy of the data cannot be assessed:

   i. The sponsor states that they evaluated folate receptor alpha (FRA) staining on a variety of normal and neoplastic tissues, including numerous cases of lung adenocarcinoma (LADC), lung squamous cell carcinoma, and ovarian cancer. The sponsors further claim that FRA staining identified 39/54 cases (72.2%) of LADC and 32/41 cases (78.8%) of ovarian cancer. Therefore, based

Table 1
Sensitivity of anti-FRA [26B3] in non-small cell lung cancer and ovarian carcinoma.

Anti-FRalpha [26B3.F2]	Lung ADC	Lung SqCC	Ovarian*
Positive Cases / Total Cases	39/54	4/37	32/41
Sensitivity	72.2%	10.8%	78.8%

   on the data provided, the sponsor claims that sensitivity of the assay in LADC and ovarian cancer as 72.2% and 78.8% respectively. However, it is not clear how truth was determined for these samples and if it is appropriate to claim these as assay "sensitivity". It appears that the sponsor is reporting the assay positivity rates based on staining a set of samples. Additionally, it is not clear if the samples that are selected for this study also include samples around the assay's clinical decision point (or cutoff). Ideally, samples around the assay cutoff should be evaluated along with adequate number of biomarker positives and negatives in analytical validation studies to demonstrate appropriate performance of the device.

   ii. Study 006 clinical trial data shows percent positivity of FRα as 99.09% for ovarian cancer (Table 7, shown below). However, as noted above, the sponsor's validation data shows a lower positivity rate of 78.8%. Therefore, the positivity data based on the trial and the studies described above do not appear to be consistent. The sponsor has not provided any explanation for this discrepant observation. Our concern is an increase in false positive rates in patients and in the risks associated.

Table 7: Alpha and Beta FR Status by Ovarian Cancer Pathology Result for Subjects
(SAS Subjects with at Least One Lesion with an Immunohistochemistry Result)

Alpha

alpha_subj	Post-Baseline Ovarian Cancer Status: No	Yes	Total
All Negative	8	1	9
	42.11	0.91	6.98
>= 1 Positive	11	109	120
	57.89	99.09	93.02
Total	19	110	129
	100.00	100.00	100.00

Fisher's exact = 0.000

iii. No line data has been provided for the results mentioned and thus could not be reviewed.

iv. The sponsor has provided reproducibility data among pathologists for only 3 cases among three independent pathologists. Out of the 3 pathologists, readings by Pathologist (b) (4) has a lot of variability in slide scoring and the readings are significantly different than the other 2 pathologists, although the sponsor reports that the M score as consistent. It is not clear how the cases were evaluated in order to determine if there was bias, for e.g., was it a blinded study, etc. Based on the scoring of staining intensity and proportion of cell staining, between-reader variability is observed. There is no additional line data to evaluate the reader reproducibility data.

Table 2
Sensitivity of anti-FRA [26B3] in non-small cell lung cancer and ovarian carcinoma.

IHC of LADC with anti-FRA [26B3]		% cells staining at each intensity				M-score
		3+	2+	1+	0	
Case 1	Pathologist (b) (4)	20	40	10	30	25
	Pathologist	20	40	10	30	25
	Pathologist	0	30	70	0	22
Case 2	Pathologist	70	20	10	0	43
	Pathologist	80	10	10	0	45
	Pathologist	95	0	0	5	48
Case 3	Pathologist	50	20	15	15	34
	Pathologist	50	20	20	10	35
	Pathologist	0	60	40	0	27

v. No validation data has been provided for Beta isoform of the folate receptor.

Summary of Discussion with CDER (INTMTG, 6/1/21):

- The Folate receptor assay will not be a companion diagnostic since this will be used as an adjunct for endpoint assessment after H&E staining to assess ovarian cancer. An extensive validation data is not needed.
- The company may not be able to provide the validation data.
- CDER thinks that the *in vitro* data in mice indicates that the antibody is specific for FR and an *in-vivo* confirmation is not needed.
- Data from both FR+ve and FR-ve patients will be used for efficacy analysis.

Based on the discussion with CDER, updated CDRH comments are being provided.

Updated Comments to CDER:

Based on the review of the above data, it appears that the sponsor has validated their device for the stated purpose. The sponsor has not provided the complete validation data. However, based on the discussions in the CDER internal meeting since this assay will not be a companion diagnostic and will be only be used as an adjunct in this trial, CDRH does not have any major concerns. However, CDRH defers to CDER to determine if additional data is needed.

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/s/

SHARON P THOMAS
10/05/2021 05:06:41 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	September 13, 2021
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214907
Product Name and Strength:	Cytalux (pafolacianine) Injection, 3.2 mg/1.6 mL (2 mg/mL)
Applicant/Sponsor Name:	On Target Laboratories
OSE RCM #:	2020-2754-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

On Target Laboratories submitted revised vial container label, single vial carton labeling and 10 vial pack carton labeling on September 3, 2021 for Cytalux (pafolacianine) injection under NDA 214907. We reviewed the revised vial container label, single vial carton labeling, and 10 vial pack carton labeling for Cytalux (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were made during a previous label and labeling review and via email communication dated August 30, 2021.[a]

2 CONCLUSION

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

[a] Kane, D. Label and Labeling Review for Cytalux (NDA 214907). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 APR 15. RCM No.: 2020-2754.

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/s/

DEVIN R KANE
09/13/2021 11:40:50 AM

HINA S MEHTA
09/14/2021 03:08:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Memorandum

Date: **September 3, 2021**

Consult Number	ICCR00058650
Consult Type	ICCR Drug-Device Combination Product
Parent Document #	NDA 214907
Requestor	Sharon Thomas
Requestor Home	CDER/OND/ORO/DROSM
Consult Home	CDRH\OPEQ\OHT4\DHT4A
Consultant	Rudy Andriani
Date Assigned	February 2, 2021
Date Due	August 27, 2021

Manufacturer/Distributor: On Target Laboratories, Inc.
Trade Name: Pafolacianine Sodium Injection (OTL38)

Recommendation: N/A

Sponsor-Provided Information
Internal Comment to Review Team

CONSULT REQUEST

"The Division of Imaging and Radiation Medicine received a new NDA, NME for pafolacianine sodium injection (OTL38) for Ovarian Ca. The Sponsor, On Target Laboratories states Quest and Medtronics (device manufactures) will file 510k submissions to use with the drug product. The 510(k) Number for Medtronic's VS3 Iridium System submission is K210265. The 510(k) submission from Quest for the Artemis Handheld Imaging System / Quest Spectrum System is pending.

The Division kindly request feedback on the camera imaging systems proposed for use in the ovarian clinical studies.
Please also identify a reviewer to attend the PDUFA related meetings for this NDA. The filing meeting is scheduled 2/9/21.
ICCR Due Date: 8/27/2021"

MATERIALS REVIEWED

- *reviewers-guide-initial-filing-29-dec-2020.pdf*

- *letter-of-authorization-quest.pdf*
- *letter-of-authorization-medtronic.pdf*
- *cover-letter-sn-0001-initial-filing-29-dec-2020.pdf*
- *packinsert-mock-final.pdf*
- *draft-labeling-text-pdf.pdf*

PROPOSED INDICATIONS FOR USE

(b) (4)

Drug: "*For adult patients with* (b) (4) *ovarian cancer as an adjunct for intraoperative identification of malignant* (b) (4) *lesions* (b) (4)

No device-related concerns identified.

PREVIOUS DEVICE-SPECIFIC COMMUNICATION
The following is provided by the sponsor in "*reviewers-guide-initial-filing-29-dec-2020.pdf*":

(b) (4)

PRODUCT DESCRIPTION
Drug:

CYTALUX (pafolacianine sodium injection)

Devices:

- Medtronic/Visionsense: VS3-Iridium
    - Previous clearance: K191851
    - Related submission: K210265
- Artemis Handheld Imaging System/Quest Spectrum System
    - Previous clearance: K143474
    - Related submission: (b) (4)

Letters of Authorization for each device submission cited above were received from the respective manufacturers.

No device-related concerns identified.

Labeling

Package Insert

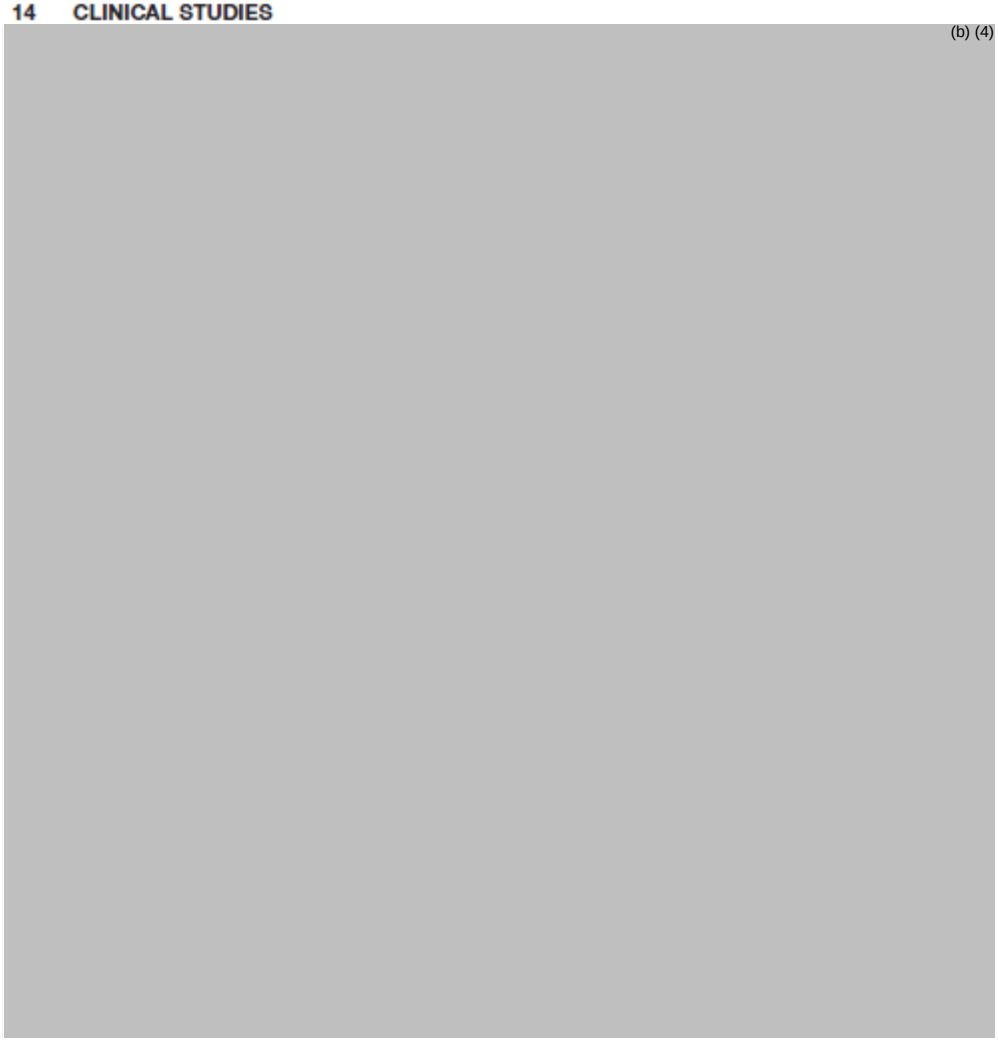
The reviewer found no concerns to raise in the relevant device-related portions of the labeling, shown below

5.3 Misinterpretation (b) (4)

Errors may occur with the use of CYTALUX™ during intraoperative (b) (4) ovarian cancer, including false negatives and false positives. (b) (4) Non-fluorescing tissue in the surgical field does not rule out the presence of ovarian cancer [see *Clinical Studies (14)*]. Fluorescence may be seen in non-cancerous tissue including areas of the bowel (b) (4) lymph nodes and inflamed tissue.

14 CLINICAL STUDIES

(b) (4)



REVIEW SUMMARY AND CONCLUSION

The information provided for review does not raise any safety concerns regarding use of the device component of this system.

Safety and performance of each device intended to be used with the proposed drug for the proposed indications will be evaluated during the 510(k) review of each proposed device.

_____

Rudy Andriani, M.S.
Lead Reviewer
CDRH/OPEQ/OHT4/DHT4A

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/s/

SHARON P THOMAS
09/13/2021 08:36:49 AM

Clinical Consultation

FROM: Mirat Shah M.D.
Medical Officer
DO1/OOD/OND/CDER

Gwynn Ison M.D.
Clinical Team Leader
DO1/OOD/OND/CDER

Laleh Amiri-Kordestani, M.D.
Division Director
DO1/OOD/OND/CDER

TO: Sharon Thomas
Regulatory Project Manager
Division of Imaging and Radiation Medicine

SUBJECT: NDA 214907

DATE CONSULT RECEIVED: February 10, 2021
DATE CONSULT DUE: June 4, 2021
DATE CONSULT COMPLETED: May 25, 2021
DATE SAFETY MEETING: NA

MATERIAL RECEIVED FOR REVIEW

- Submission package for NDA 214907

REQUESTED ACTION

DIRM requests DO1 guidance regarding their review of pafolacianine sodium (OTL38) under NDA 214907. OTL38 is an NME and the applicant, On Target Laboratories, is seeking an indication for its use as an optical imaging agent to guide (b) (4) surgery in patients with ovarian cancer.

The specific consult questions is:

1. If there is a current clinical need to further augment the outcome in patients with epithelial ovarian cancer (EOC) who undergo debulking surgery along with systemic chemotherapy.

DO1 RESPONSE

Thank you for allowing us to participate in this consultation.

DO1 comments:

1. **Response to consult question:** The specific consult question from DIRM appears to be whether there is an unmet medical need for patients with EOC who are undergoing debulking surgery along with systemic chemotherapy. DO1 considers patients with EOC who are undergoing debulking surgery along with systemic chemotherapy to have an unmet medical need for the following reasons:
    a. EOC is typically diagnosed at an advanced stage.
    b. Five-year survival for advanced-stage EOC is low and better therapies are needed.
    c. Treatment for advanced-stage EOC is typically debulking surgery and adjuvant systemic chemotherapy with bevacizumab (if eligible), followed by maintenance treatment with bevacizumab. Some patients may also be candidates for maintenance treatment with a PARP inhibitor.
    d. Recurrence following this treatment paradigm is common.
    e. Recurrent disease is not curable.

    EOC makes up approximately 90% of total cases of ovarian cancer in the U.S. each year and is typically diagnosed at an advanced stage.[1,2] At diagnosis, 16% of patients have disease that is localized/confined to the ovary (Stage I-II), 21% of patients have regional disease (stage III), and 57% of patients have distant disease (stage IV).[3] Five-year overall survival decreases with increasing stage. Five-year OS is 93% for patients with localized disease, 75% for patients with regional disease, and only 30% for patients with distant disease.[3] Patients who receive debulking surgery along with systemic chemotherapy will typically have disease that is stage IB-IV.[4] Patients with higher-stage disease have a higher likelihood of recurrence, and EOC is largely not curable in the recurrent setting. Better treatments to improve OS for EOC are needed.

2. **DO1 comment:** Regarding folate receptor- alpha (FRα)-positive ovarian cancer, DO1 notes that approximately 70% of primary EOC is FRα-positive, and therefore, approximately 30% of primary EOC is FRα-negative.5 OTL38's activity is mediated through FRα. However, the Applicant is not proposing to screen patients for tumor FRα-positivity to receive treatment with OTL38. Therefore, this may lead to false negative findings. DO1 defers to DIRM regarding this issue and whether a companion diagnostic may be needed.

REVIEW OF MEETING PACKAGE

OTL38 (CYTALUX™) is folic acid analog imaging agent. The Applicant, On Target Laboratories, is seeking the following indication for its use:

CYTALUX™ is an optical imaging agent indicated for adult patients with (b) (4) (b) (4) *ovarian cancer as an adjunct for intraoperative identification of malignant* (b) (4) (b) (4) *lesions* (b) (4)

<u>Background and Rationale</u>

Per the Applicant, OTL38 is a folic acid analog conjugated with an indole cyanine green-like dye. It binds to the folate receptor-alpha (FRα) and can act like an imaging agent in patients with tumors over-expressing FRα, including ovarian cancer. When OTL38 binds to FRα, it emits light with wavelengths in the near-infrared (NIR) spectrum which can be captured by an imaging probe during surgery. Typically, folate distributes to all healthy tissues initially and then is eliminated within 2-3 hours, but areas with high density of FRα (like tumors) will retain folate. The renal proximal tubules express FRα and so OTL38 may also be taken up by the kidneys.

Registrational Trial

The Applicant conducted a phase 3, multicenter, randomized, single dose, open-label trial to examine the safety and efficacy of a single dose of OTL38 for intra-operative imaging of FRα-positive ovarian cancer in patients scheduled for primary surgical cytoreduction, interval debulking surgery, or surgery for recurrent ovarian cancer.

Objectives and Endpoints

The primary objective was to confirm the efficacy of OTL38 in combination with NIR fluorescent light to detect additional FRα- positive ovarian cancer lesions not detected by palpation and visualization under normal light. ("Visualization under normal light" refers to visual inspection by the surgeon during surgery.) The secondary objectives also relate to examining the performance of OTL38/NIR to detect ovarian cancer lesions.

Primary Endpoint:

- Proportion of patients with at least one evaluable FRα-positive ovarian cancer lesion confirmed by central pathology detected by OTL38/NIR but not under normal light/palpation

Secondary Endpoints:

- Proportion of patients in whom all lesions detected by OTL38/NIR were histologically negative.
- Proportion of lesions histologically confirmed as ovarian cancer that were detected by OTL38/NIR (sensitivity)
- Proportion of lesions identified by OTL38/NIR that were histologically negative

Trial Design

All patients enrolled to the study would have received an assessment based on medical history, physical exam, labs, and imaging evaluation (CT, PET/CT, MRI) as per standard-of-care. The surgeon would use this information to form the pre-NIR surgical plan. Patients would receive OTL38 and undergo normal light evaluation, and all suspicious lesions would be recorded. The surgeon could also use this information to modify the pre-NIR surgical plan. Then, the majority of patients would undergo NIR fluorescent light imaging, except 5% of patients who would be randomly assigned to a no NIR fluorescent imaging group. Patients "randomized" to NIR fluorescent imaging would have this performed prior to surgical procedure and immediately after but prior to surgical closure. Any lesions identified with NIR were recorded in the eCRF and

evaluable lesions were those that would not have been removed based on the pre-NIR surgical plan. Patients were followed for safety with visits on post-op Day 7, Day 28, and 6 months later. The purpose of randomization in this study is unclear as the primary and secondary endpoints only take into account patients on the OTL38/NIR arm.

Key Inclusion criteria

- Female patients with a diagnosis or high clinical suspicion of EOC, planned for primary surgical cytoreduction, interval debulking, or surgery for recurrent disease
- Scheduled for laparotomy for debulking surgery **or** scheduled for laparoscopy and preauthorized to undergo laparotomy for debulking if cancer detected on laparoscopy

Key Exclusion criteria

- Known FRα-negative ovarian cancer
- Planned debulking via laparoscopy with no intent of laparotomy
- Patients with disease known to be inoperable

Of note, although known FR-negative ovarian cancer is an exclusion criterion, having an FRα-positive tumor is NOT an inclusion criterion and tumors are not being evaluated for FRα-positivity as part of this trial.

Dosing Regimen and Assessments

Patients were to receive OTL38 0.025 mg/kg as a single dose at least one hour prior to initiation of NIR fluorescent imaging.

Statistical Plan

The primary endpoint was the proportion of patients with at least one evaluable FRα-positive ovarian cancer lesion confirmed by central pathology detected by OTL38/NIR but not under normal light/palpation. The null hypothesis was that the proportion of such patients would be 10%. The null hypothesis would be rejected if the observed proportion of patients was greater than 10% as tested using an exact binomial test with a two-tailed alpha level of 0.05.

Results

178 patients were enrolled to the study of whom 150 patients received OTL38. Out of these 150 patients, 134 patients were randomly assigned to the NIR fluorescent imaging group and 6 patients were randomly assigned to normal light without NIR. 10 patients were not assigned to either group. There were 109 patients in the “full analysis set: FAS” which includes patients who received OTL38, received NIR fluorescent imaging, and had central pathology and histologic confirmation for one lesion detected under NIR or normal light. The per protocol analysis set (PPAS) set includes patients from the FAS population who met all eligibility criteria, had no major protocol deviations, received at least 50% of the OTL38 dose, and had NIR no earlier than 1 hour after OTL38 dose. The acceptability of the FAS and PPAS populations are beyond the scope of this consult.

Patient characteristics are shown in this table which has been modified from the Applicant's CSR:

Full Analysis Set (FAS) Disease Characteristics following Debulking Surgery

Characteristic	N= 109 N (%)
Post-surgical diagnosis	109
Ovarian cancer	92 (84)
Primary Peritoneal cancer	7 (6)
Fallopian tube cancer	3 (3)
No evidence of disease	3 (3)
Other	4 (4)
Histologic Type	105
Serous adenocarcinoma	72 (66)
Endometrioid carcinoma	2 (2)
Adenocarcinoma	6 (6)
Mucinous adenocarcinoma	1 (1)
Clear cell carcinoma	3 (3)
Other	21 (19)
Stage at Diagnosis (Post-Surgery)	106
I	0 (0)
IA	1 (1)
IB	0 (0)
IC	4 (4)
II	1 (1)
IIA	2 (2)
IIB	1 (1)
IIC	2 (2)
III	3 (3)
IIIA	6 (6)
IIIB	18 (17)
IIIC	40 (37)
IV	16 (15)
Unknown	12 (11)

For the primary endpoint in the FAS population, 33% (36/109 patients, 95% CI: 24, 43) of patients had a lesion detected with OTL38/NIR but not under normal light which was confirmed as ovarian cancer. This represented an improvement compared to the Applicant's pre-specified threshold of 10%. From my review, it is unclear if this benchmark was agreed-upon by DIRM. For the secondary endpoints, 25% (27/109 patients, 95% CI: 18, 34) of patients had lesion(s) detected by OTL38/NIR only which were histologically negative. The sensitivity of the OTL38/NIR detection method was estimated at 83% (95% CI: 74, 89). The proportion of lesions which were detected by OTL38/NIR and histologically negative was 33% (95% CI: 26, 41).

References[1]

1. Roett MA, Evans P. Ovarian cancer: an overview. *Am Fam Physician.* 2009;80(6):609-616.
2. Society AC. Cancer Facts and Figures 2021. 2021.
3. National Cancer Institute. Surveillance E, and End Results Program. Cancer Stat Facts: Ovarian Cancer. 2021.
4. Network NCC. Ovarian Cancer Version 1.2021- February 26, 2021. 2021.

[1]

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/s/

MIRAT S SHAH
08/10/2021 12:31:22 PM

GWYNN ISON
08/10/2021 12:51:06 PM

LALEH AMIRI KORDESTANI
08/10/2021 01:07:27 PM

Consult Memorandum

Date:	06/03/2021
To:	Sharon Thomas, CDER/OND/ORO/DROSM Joseph Rajendran, CDER/OND/OSM/DIRM
From:	Arpita Roy, Scientific Reviewer, MPCB/DMGP/OHT7/CDRH
Through:	Shyam Kalavar, Team Lead, MPCB/DMGP/OHT7/CDRH Soma Ghosh, Branch Chief, MPCB/DMGP/OHT7/CDRH Reena Philip, Director, DMGP/OHT7/CDRH
ICC Number:	ICCR# 00084169; ICC2100438
Protocol Title:	Study OTL-2016-OTL38-006 (Study 006) A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection (OTL38) for Intraoperative Imaging of Folate Receptor Positive Ovarian Cancer
Subject:	Consult request- NDA 214907
Drug Name:	Pafolacianine sodium injection (OTL38)
Drug Sponsor	On Target Laboratories, Inc.
Biomarker(s):	Folate Receptor (FR, alpha and beta isoforms)
Device Sponsor:	Biocare Medical Folate Receptor alpha IHC Assay kit
Related Submissions:	None

I. BACKGROUND and PURPOSE

Expression of FRα occurs frequently, especially in the common high-grade, high-stage serous epithelial ovarian tumors that are most likely to recur. Hence, FR-based diagnostic and therapeutic strategies have been and continue to be used to identify malignant tissue in the treatment of ovarian cancer. On Target Laboratories, Inc. (OTL) has developed pafolacianine sodium injection (OTL38), a folic acid analogue conjugated with an indole cyanine green-like dye as a tumor-specific imaging agent.

The efficacy of pafolacianine sodium injection was confirmed in 1 pivotal study (Phase 3 Study 006) and 1 supporting study (Phase 2 Study 003). For Study 006, the primary efficacy endpoint was the proportion of patients with at least 1 evaluable FR+ ovarian cancer lesion confirmed by central pathology (standard of truth) that was detected using the pafolacianine and fluorescent light but not under normal light or palpation.

II. CDRH RESPONSE TO CDER QUESTIONS:

IHC was performed in addition to histopathology to establish the primary efficacy end point of having at least one ovarian cancer lesion identified using Pafolacianine and NIR light that was not

identified by standard of care normal light or palpation during debulking surgery. OTL used a commercially available IHC kit from Biocare Medical Folate Receptor alpha IHC Assay kit.

CDER requested CDRH to provide comments for the following:

- Regulatory status of IHC tests for FR alpha and beta expression
  - Explain what components of the IHC tests are FDA cleared
- CDRH guidance in assessing/analyzing the FR IHC assay data and acceptability of sponsor responses to CDER comments to the sponsor as follows:
  - Provide the results of your analyses that validate the accuracy of the FR IHC testing as conducted by the central pathology laboratory for the purpose of the truth standard

CDRH comments to CDER:

1. There are no FDA approved or cleared IHC assays to assess the expression of folate alpha or beta receptors.

2. Based on the concerns mentioned below the accuracy of the data cannot be assessed:

   i. The sponsor states that they evaluated folate receptor alpha (FRA) staining on a variety of normal and neoplastic tissues, including numerous cases of lung adenocarcinoma (LADC), lung squamous cell carcinoma, and ovarian cancer. The sponsors further claim that FRA staining identified 39/54 cases (72.2%) of LADC and 32/41 cases (78.8%) of ovarian cancer. Therefore, based

Table 1
Sensitivity of anti-FRA [26B3] in non-small cell lung cancer and ovarian carcinoma.

Anti-FRalpha [26B3.F2]	Lung ADC	Lung SqCC	Ovarian*
Positive Cases / Total Cases	39/54	4/37	32/41
Sensitivity	72.2%	10.8%	78.8%

   on the data provided, the sponsor claims that sensitivity of the assay in LADC and ovarian cancer as 72.2% and 78.8% respectively. However, it is not clear how truth was determined for these samples and if it is appropriate to claim these as assay "sensitivity". It appears that the sponsor is reporting the assay positivity rates based on staining a set of samples. Additionally, it is not clear if the samples that are selected for this study also include samples around the assay's clinical decision point (or cutoff). Ideally, samples around the assay cutoff should be evaluated along with adequate number of biomarker positives and negatives in analytical validation studies to demonstrate appropriate performance of the device.

   ii. Study 006 clinical trial data shows percent positivity of FRα as 99.09% for ovarian cancer (Table 7, shown below). However, as noted above, the sponsor's validation data shows a lower positivity rate of 78.8%. Therefore, the positivity data based on the trial and the studies described above do not appear to be consistent. The sponsor has not provided any explanation for this discrepant observation. Our concern is an increase in false positive rates in patients and in the risks associated.

Table 7: Alpha and Beta FR Status by Ovarian Cancer Pathology Result for Subjects
(SAS Subjects with at Least One Lesion with an Immunohistochemistry Result)

Alpha

alpha_subj	Post-Baseline Ovarian Cancer Status: No	Yes	Total
All Negative	8	1	9
	42.11	0.91	6.98
>= 1 Positive	11	109	120
	57.89	99.09	93.02
Total	19	110	129
	100.00	100.00	100.00

Fisher's exact = 0.000

iii. No line data has been provided for the results mentioned and thus could not be reviewed.

iv. The sponsor has provided reproducibility data among pathologists for only 3 cases among three independent pathologists. Out of the 3 pathologists, readings by Pathologist (b) (4) has a lot of variability in slide scoring and the readings are significantly different than the other 2 pathologists, although the sponsor reports that the M score as consistent. It is not clear how the cases were evaluated in order to determine if there was bias, for e.g., was it a blinded study, etc. Based on the scoring of staining intensity and proportion of cell staining, between-reader variability is observed. There is no additional line data to evaluate the reader reproducibility data.

Table 2
Sensitivity of anti-FRA [26B3] in non-small cell lung cancer and ovarian carcinoma.

IHC of LADC with anti-FRA [26B3]		% cells staining at each intensity				M-score
		3+	2+	1+	0	
Case 1	Pathologist (b) (4)	20	40	10	30	25
	Pathologist	20	40	10	30	25
	Pathologist	0	30	70	0	22
Case 2	Pathologist	70	20	10	0	43
	Pathologist	80	10	10	0	45
	Pathologist	95	0	0	5	48
Case 3	Pathologist	50	20	15	15	34
	Pathologist	50	20	20	10	35
	Pathologist	0	60	40	0	27

v. No validation data has been provided for Beta isoform of the folate receptor.

Summary of Discussion with CDER (INTMTG, 6/1/21):

- The Folate receptor assay will not be a companion diagnostic since this will be used as an adjunct for endpoint assessment after H&E staining to assess ovarian cancer. An extensive validation data is not needed.
- The company may not be able to provide the validation data.
- CDER thinks that the *in vitro* data in mice indicates that the antibody is specific for FR and an *in-vivo* confirmation is not needed.
- Data from both FR+ve and FR-ve patients will be used for efficacy analysis.

Based on the discussion with CDER, updated CDRH comments are being provided.

Updated Comments to CDER:

Based on the review of the above data, it appears that the sponsor has validated their device for the stated purpose. The sponsor has not provided the complete validation data. However, based on the discussions in the CDER internal meeting since this assay will not be a companion diagnostic and will be only be used as an adjunct in this trial, CDRH does not have any major concerns. However, CDRH defers to CDER to determine if additional data is needed.

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/s/

SHARON P THOMAS
08/04/2021 05:17:59 PM

Clinical Inspection Summary

Date	7/14/21
From	Christian Shenouda, MD Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Joseph Rajendran, M.D., Medical Officer Venkata Anand Mattay, MD, Clinical Team Leader Sharon Thomas, Regulatory Program Manager Division of Imaging and Radiation Medicine (DIRM)
NDA	NDA 214907
Applicant	On Target Laboratories, LLC
Drug	Pafalocianine sodium injection; OTL38 injection
NME	Yes
Proposed Indications	For adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant (b) (4) lesions (b) (4)
Consultation Request Date	2/16/2021
Summary Goal Date	7/29/2021
Action Goal Date	8/27/2021
PDUFA Date	8/29/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators Drs. Wenham and Tanyi and the CRO, (b) (4) were inspected in support of a New Drug Application (NDA 214907). The inspections of (b) (4) and Dr. Tanyi did not reveal any significant GCP-related concerns regarding their conduct of the pivotal study, Protocol OTL-2016-OTL38-006. The inspection of Dr. Robert Wenham revealed several issues related to preparation of the investigational product (IP), start and stop time of the OTL-38 infusion documentation, concomitant medication usage, and a number of other protocol violations, which included underreporting of non-serious adverse events. The sponsor has since communicated with FDA to update the NDA to include all unreported adverse events from this site. There are otherwise no concerns regarding the reliability of the data from this site.

For both clinical investigator inspections, the data for lesion detection was verifiable, i.e., there were no discrepancies identified between the source data and the data line listings provided by the sponsor with regard to lesion counts identified for both normal light and those visualized with the fluorescence camera system. Per the protocol, the number and site of lesions detected with normal light would be recorded, followed by the number and site of lesions detected using the IP. The lesions were then resected and sent to a central pathology laboratory for histological analysis. The primary endpoint utilized the number of histologically confirmed lesions to compare efficacy of the IP to normal light. However, a primary endpoint variable, the central pathology reads for the lesions that were detected using the combination of OTL38

and NIR fluorescent light, could not be adequately verified at the clinical investigator sites because the primary endpoint variable was captured at the central laboratory and there were no formal pathology laboratory reports available at the two investigator sites. The pathology reads were captured in an Excel spreadsheet. Specifically, blinded pathologists were provided an Excel spreadsheet with prepopulated metadata, such as subject ID, specimen number, and site of collection. The pathologists then entered their read of the specimen into the Excel spreadsheet. The Excel spreadsheet did not contain acceptable audit trails to record who entered specific data, when changes were made after the original entry including date of modification, why changes were made, and who made them. As a result, it is difficult to confirm the potential data integrity and reliability of the submitted information for the primary efficacy endpoint itself as there were no supportive source data available to substantiate what has been reported in the Excel spreadsheet.

OSI discussed steps on how to address the potential data integrity and reliability concerns regarding the reported primary efficacy endpoint with the review division. To address these concerns, the review division has requested that the sponsor randomly select H&E slides, perform repeat pathology reads, and provide a concordance report which compares these follow up reads to the initial pathology reads reported in the Excel spreadsheet that were submitted to the Agency.

II. BACKGROUND

Over 90% of ovarian epithelial cancers express a folate receptor (FR), a folate binding protein. Pafalocianine sodium (OTL-38) is a folic acid analog ligand conjugated with an indole cyanine-like green dye. The investigational product is to be administered in a single dose over approximately 60 minutes and at least one hour prior to the operative procedure to aid in identification and removal of folate receptor positive (FR+) lesions.

Protocol OTL-2016-OTL38-006

Title: "A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection (OTL38) for Intra-operative Imaging of Folate Receptor Positive Ovarian Cancer"

Subjects: 150 subjects

Sites: 11 sites (10 sites in the United States and 1 site in the Netherlands)

Study Initiation and Completion Dates: 14 March 2018 – 16 April 2020

Summary
This was a phase 3, randomized, multicenter, single dose, open-label study designed to investigate the safety and efficacy of OTL38 as an adjunct for intra-operative imaging of folate receptor positive (FR+) ovarian cancer in patients diagnosed with, or with high clinical suspicion of, ovarian cancer who are scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery. All subjects who participated in the study were expected to receive OTL38 (administered intravenously over one hour) and

undergo normal intraoperative light evaluation. To control for possible "under-calling" of lesions, 5% of patients were randomly assigned to a no fluorescent imaging group in a blinded fashion. Of note, dosing occurred prior to randomization in this study.

All subjects first underwent an evaluation by normal light, and all suspicious lesions were recorded. Following the normal light assessment, but prior to any surgical removal of lesions or the use of NIR fluorescent light imaging, patients were randomly assigned to either undergo NIR fluorescent imaging (95% of subjects) or normal light only (5% of subjects).

Lesions identified under NIR imaging were recorded in the eCRF. Evaluable lesions were defined as follows: lesions that did not appear on an organ or tissue that was intended for removal based on the pre-fluorescence surgical plan regardless of the absence or presence of tumor. Lesions identified under normal light were compared to OTL38-enhancing lesions identified under NIR fluorescent light.

After collection of surgical specimens, the samples were sent to a central pathology laboratory, (b) (4) Each lesion was reviewed by two blinded, independent pathologists to evaluate for the presence of malignant cells. The primary efficacy endpoint was the proportion of patients with at least one evaluable folate receptor positive (FR+) ovarian cancer lesion confirmed by central pathology (standard of truth) that was detected using the combination of OTL38 and NIR fluorescent light but not under normal light or palpation.

Rationale for Site Selection
The following clinical investigator (CI) site was chosen for inspection using a risk-based approach, including number of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

III. INSPECTION RESULTS

The clinical investigator inspections performed verification of lesion counts and locations. The details of the pathology reads were not available for review and verification during inspection as they were done at the central laboratory. According to the sponsor response to an IR to obtain certified copies of the pathology reads, the sponsor informed FDA (in the sponsor's 4 June 2021 IR response) that:

(b) (4)

The sponsor, in their 10 June 2021 IR response, further clarified that:

(b) (4)

It was again made clear that there were no pathology laboratory reports generated and that therefore the source for pathology reads appeared to be the Excel spreadsheets. Through a subsequent IR, it was found out that "all pathology slide samples are archived at (b) (4) Each slide can be traced to the appropriate patient ID, which was included in the NDA."

In a meeting with DIRM, on 17 June 2021, OSI further explained the issue, and we summarized our concerns that the Excel spreadsheet does not contain adequate audit trails, so there is no record of who entered what data and when as well as if any changes were made after the original entry (including who made the change, when, and why). As such, the reported primary endpoint itself could not be properly verified to ensure reliability of the data.

The review division and OSI devised a plan outlined in the "Late Cycle Review Meeting General Advice Letter" from 23 June 2021, that stated:

> Our review to date has determined that the primary endpoint cannot be verified due to lack of certified pathology reports for audit and we propose the following strategy:
>
> 1. Provide the total number of lesions removed as part of Study OTL-2016-OTL36-006.
> 2. Identify a randomized sample (of at least 10%) from the entire pool of lesions (H&E slides only).
> 3. Provide details about the algorithm used to choose proportional to study participants with more lesions versus with less lesions.
> 4. Provide metadata and a pathologist assessment of tumor status for all identified randomized sample from the entire pool of lesions.
> 5. Provide pathology report for each H&E slide read by a pathologist (either new or a previous reader) blinded to all information including previous reads.
> 6. Provide concordance report between the initial read and re-read and provide 95% interval estimates of the concordance for review.

The sponsor responded to the IR on 28 June 2021 and included a draft "Concordance Sampling and Analysis Plan." At the time of the writing of this CIS, this plan was being finalized between the sponsor and review division.

Additionally, the review division communicated with the sponsor regarding underreporting of adverse events in the "General Advice Letter" from 23 July 2021. The following text was included in the letter:

> During the GCP inspection, it was noted there were discrepancies between reported adverse events to FDA and those in patients/source records. Provide details and a complete list of all subjects impacted with under reporting of adverse events in all clinical trial sites.

During a subsequent teleconference held on 25 July 2021, it was agreed that the sponsor would provide updated information regarding all adverse events for Site #5. The sponsor provided a response dated 2 July 2021, in which supposedly unreported AEs were listed. However, the list also included AEs that had been previously reported. Of note, all the unreported events were non-serious and deemed unrelated to the IP.

1. (b) (4)

For Protocol OTL-2016-OTL38-006, (b) (4) a CRO, was responsible for oversight of the clinical sites, including monitoring, protocol specific training, data evaluation, and drug safety. (b) (4) was also responsible for the selection of clinical investigators, with input and final decision by the sponsor. The trial included eleven domestic clinical sites, with ten of the sites overseen by (b) (4) The site not overseen by (b) (4) was in the (b) (4)

The inspection reviewed the firm's organizational charts, study personnel records, contracts and work orders, standard operating procedures, study specific procedures, protocol deviation reporting documentation, monitoring documentation, and procedures for handling protocol deviations.

More specifically, the inspection reviewed standard operating procedures (SOP) that describe how to identify, report, evaluate, and solve issues with sites who are non-compliant. (b) (4) did not terminate or close any sites. Ten of the eleven clinical sites participating in the OTL-2016-OTL38-006 protocol were reviewed, and it was noted that Site #8 was never activated, Site #11 withdrew after activation, and Site #12 was never activated.

The inspection also examined monitoring and safety plans and the applicable monitoring procedures along with records documenting site initiation visits, monitoring reports, actions items, protocol deviations, and serious adverse events. There were no deficiencies noted. (b) (4) conducted site initiation visits (SIV) for all sites, and no significant issues were noted during those inspections.

The inspection confirmed that site monitors conducted quality control assessments by a comparison of individual subject records and other source documents with electronic case report forms (eCRFs) submitted to the sponsor electronically. The monitors verified the data against supporting documents such as medical charts, laboratory reports, and progress notes maintained by the site.

(b) (4) was responsible for ensuring all adverse events were documented and reviewed by (b) (4) safety management team using the safety management plan for the study. Review of adverse events and serious adverse events during the inspection noted no underreporting of adverse events, and serious adverse events were submitted to the IRBs in a timely manner. Protocol deviations were evaluated, and the majority of deviations for all sites were due to missed assessments. All missed assessments were reported as protocol deviations.

2. **Robert Wenham**
   Site #2
   Moffitt Cancer Center
   12902 Magnolia Dr
   Tampa, FL 33612
   Inspection Dates: 4/5/2021 – 4/16/2021

   At this site for Protocol OTL-2016-OTL38-006, there were 33 subjects screened, 30 dosed, and 28 subjects completed the study. According to the sponsor's data line listings, Subject (b) (6) was dosed and randomized, but due to problems with the imaging system, the protocol assessments were not performed, and the subject was classified as not completing the study. Subject (b) (6) did not complete the study due to vomiting classified as a severe adverse event; this subject had been dosed with the IP.

   Records reviewed during the inspection included financial disclosures, Form FDA 1572s, informed consent forms, adverse event reporting, investigational product handling (accountability, storage, dispensation, infusion), protocol deviations, inclusion/exclusion criteria, primary/secondary efficacy data, reason for discontinuation/withdrawals, concomitant medications, study monitoring reports and IRB communications/approvals.

   The data for lesion detection was verifiable, i.e., there were no discrepancies identified between the source data and the data line listings provided by the sponsor with regard to lesion counts identified for both normal light and those visualized with the fluorescence camera system. As described above, the pathology assessments were done via a central laboratory, and this data could not be verified during this inspection.

   The inspection noted that there was underreporting of adverse events in 4 of 10 (40%) of subject records examined. The adverse events were deemed unrelated to the investigational product, and none of these were serious adverse events. These events included episodes of emesis, constipation, depression, and anxiety. As noted above, the sponsor was asked to provide an updated listing of unreported adverse events at this

site. However, the submitted list also included AEs that had been previously reported. There was only one AE that had not been previously reported and had not been discovered at the inspection (back pain in Subject (b) (6)

Reviewer's comment: We recommend that the review division include these unreported, non-serious adverse events in their safety evaluation of the investigational product.

There were some investigational product (IP) documentation issues observed regarding the preparation of the IP. This included the fact that the "vortex time" was missing in 20 of 31 subject records examined. The protocol specified that the product should be "vortexed" for 60 seconds.

Reviewer's comment: This appears to be a documentation issue. The "vortex time" in 20 of 31 subjects was not properly documented to confirm the preparation complied with the protocol. The lack of documentation was attributed to use of forms which did not specify vortex time recording and as such, it is unclear if the procedure was performed according to the protocol for these subjects.

Additionally, infusion of OTL-38 one hour prior to imaging was not documented in 2 of 11 subject records examined. Section 5.5.4 of the protocol specified that the product should be administered over approximately 60 minutes and completed at least one hour prior to intraoperative imaging. The CI attributed this protocol violation to administration of the medication in two environments: the pre-operative holding area and the Clinical Research Unit, the former not having research-trained staff.

Reviewer's comment: The start and stop time of the OTL-38 infusion should have been documented in all the subjects with data showing that imaging was done one hour after the completion of medication administration. In these two cases, the infusion start times were documented, but there is missing documentation to show what time the camera system was turned on during the surgery. The CI attribution of the inspectional findings is inadequate. Although this is a regulatory violation, the finding occurred only in 2 of the patients, and it does not appear to be clinically significant.

There were errors in the documentation of concomitant medication usage in 7 out of 7 subject records reviewed. The errors included missing medication and inaccuracies in dosing (amount and/or frequency) for multiple medications. This was likely the result of transcription errors when the data was transferred from the EMR to the eCRF.

Reviewer's comment: None of these discrepancies involved prohibited concomitant medications. There was only one unreported medication, magnesium sulfate in Subject (b) (6) All the other discrepancies involved inaccuracies in dosing. In the opinion of this reviewer, the dosing discrepancies were not significant enough to change the overall efficacy or safety evaluations of the investigation product.

3. **Janos Tanyi**
Site #5
University of Pennsylvania Health System
3400 Civic Center Blvd
Philadelphia, PA 19104
Inspection Dates: 5/10/2021 – 5/14/2021

At this site for Protocol OTL-2016-OTL38-006, there were 32 subjects screened, 28 subjects enrolled, 25 subjects were dosed. Three subjects withdrew consent prior to dosing (Subjects (b) (6) (b) (6) and (b) (6) Of the 25 subjects dosed, 21 subjects were randomized, and 21 subjects completed the study. (Subjects (b) (6) (b) (6) and (b) (6) were dosed and but not randomized due to disease classified as too extensive; subject (b) (6) had their surgery cancelled for unclear reasons but was dosed with the investigational product.)

Records reviewed during the inspection include informed consent forms (ICFs), regulatory binders for IRB communication/approvals, Form 1572s, financial disclosure forms, drug accountability logs, monitoring reports, subject source documents in hard copies and within the electronic medical records, laboratory reports, study end point data and questionnaires, adverse event logs, concomitant medication logs and deviation logs.

The data for lesion detection was verifiable, i.e., there were no discrepancies identified between the source data and the data line listings provided by the sponsor with regard to lesion counts identified for both normal light and those visualized with the fluorescence camera system.

There was no evidence of under-reporting adverse events. There were three SAEs at the site that were deemed as unrelated to the study drug and these SAE were provided for review in the application materials. Subject (b) (6) had lower abdominal pain, Subject (b) (6) had a pleural effusion, and Subject (b) (6) had pneumonia; all three required hospitalization for their condition.

There were several minor protocol deviations noted related to missed assessments and out of window vital sign assessments. The protocol dictates that vital signs must be taken 15 minutes prior to OTL38 infusion. Six subjects (Subjects (b) (6) (b) (6) (b) (6) (b) (6) (b) (6) and (b) (6) had their vital signs taken outside of the 15-minute window. Data available show that pre-infusion vital signs were taken up to 65 minutes prior to the infusion. Protocol deviations for these subjects were reported to the Agency in the application materials. The clinical investigator (CI) attributed this to a lack of research-trained nursing staff. Missed assessments included screening magnesium levels in one subject, liver function tests on day 7 for one subject, and EKGs not done in two subjects on day 7. The CI acknowledged the missed laboratory assessments and stated staff that were re-educated about the protocol when the deviations were noted.

Reviewer's comment: The protocol deviations (out of window vital signs collection and missed assessments) are regulatory violations. Based on the information available for review, the missed assessments are sporadic. Although the deviations were sporadic, study participants would have been exposed to an unreasonable risk of illness or injury. The CI attribution of the inspectional findings is inadequate.

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Division of Clinical Compliance Evaluation
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Review

Date: June 10, 2021 **Date consulted:** February 19, 2021

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Medical Imaging and Radiation Medicine (DIRM)

Drug: CYTALUX (pafolacianine sodium) injection

NDA: 214907

Applicant: On Target Laboratories, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant (b) (4) lesions (b) (4)

Materials Reviewed:

- DPMH consult request dated February 19, 2021, DARRTS reference ID 4749870
- NDA 214907 submitted December 29, 2020
- DPMH memorandum regarding input for Type B Pre-NDA Sponsor meeting, IND 118255, November 13, 2020, DARRTS reference ID: 4718250

- Information Request (IR) response from applicant, dated May 7, 2021

Consult Question: "DIRM would like DPMH to assist with the labeling review."

INTRODUCTION AND BACKGROUND

On December 29, 2020, On Target Laboratories submitted a 505(b)(1) new drug application for CYTALUX (pafolacianine sodium) injection, a new molecular entity. Pafolacianine sodium injection (OTL 38) is a folic acid analog conjugated with a fluorescent dye which targets and selectively illuminates ovarian epithelial cancer cells and may be used as an adjunct for intraoperative identification of malignant tissue. On February 19, 2021, DIRM consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Pafolacianine sodium injection is an optical imaging agent proposed for use in adult patients with known or suspected ovarian cancer as an adjunct for intraoperative identification of malignant (b) (4) lesions (b) (4). Cytalux is to be used with a designated camera imaging system.
- Pafolacianine sodium is not currently approved in any country. Targeted optical imaging has been applied in multiple indications. Indocyanine green and methylene blue are the only two near-infrared (NIR) fluorescent dyes approved by the FDA.[1]
- The applicant received Orphan Drug Designation (2014) and Fast Track designation (2016) within the ovarian cancer indication.
- DIRM granted a waiver of reproductive and developmental toxicity studies under IND 118,215 (2015) because the agency generally does not require reproductive toxicity studies for single-use imaging products. Nevertheless, the applicant submitted nonclinical reproductive and developmental toxicity studies which were already completed.
- November 13, 2020: At a Pre-NDA Type B Industry meeting, the applicant asked about the appropriateness of including animal data in Section 8. DPMH-Maternal Health Team provided input that data from embryo-fetal studies may be included in Subsection 8.1 or Section 5 depending on the level of concern for toxicity.
- On April 27, 2021, DPMH submitted an IR to the applicant regarding the literature search and pharmacovigilance database. On May 7, 2021, the applicant submitted their response.

Drug Characteristics[2]

- Drug class: optical imaging agent
- Mechanism of action[3]: Pafolacianine binds specifically and with high affinity to the folate receptor alpha (FRα), excites to light between the wavelengths of 760-776 nm, and fluoresces at wavelengths in the NIR spectrum. Following intravenous (IV) administration, the drug product OTL38 is distributed throughout the body. It is rapidly cleared from the plasma but is retained in tissues where it is bound to FRα receptors. FRα

[1] Debie P, Hernot S. Emerging fluorescent molecular tracers to guide intra-operative surgical decision-making. Front Pharmacol. 2019;10:510. doi:10.3389/fphar.2019.00510

[2] Applicant's proposed labeling for CYTALUX, NDA 214907

[3] Information based on document provided by Pharmacology/Toxicology

is normally found on the apical surfaces of several epithelial cells but most of these receptors are inaccessible to parenterally administered folate conjugates.[4] In a pharmacokinetic study in 16 healthy volunteers administered a single IV infusion of pafolacianine sodium, only 35% of the drug was excreted 3-5 weeks post dose.[5]

- Molecular weight: 1414 Daltons
- Half-life: increases with dose; 0.4 hours at the proposed dose of 0.025 mg/kg. While pafolacianine sodium clears rapidly from receptor-negative tissues, , it is retained for weeks in tissues with FRα.[6]
- Plasma protein binding: 94%
- Dosing: A single intravenous infusion of 0.025mg/kg diluted with 250 ml 5% Dextrose Injection, administered over 60 minutes in adults, 1-(b) (4) hours prior to (b) (4)
- Most common adverse reactions: nausea, vomiting, abdominal pain, and infusion reactions
- Folate, folic acid, or folate-containing supplements should not be taken within 48 hours before administration of CYTALUX because folate supplements may block access to folate receptors.

Reviewer comment: DPMH discussed the tissue half-life of pafolacianine with the Clinical Pharmacology team. It is unknown how long pafolacianine resides in the body. Based on the mass balance study, only 35% of the drug was excreted from the body after approximately one month so it could theoretically take Cytalux as long as five months to clear from the body.

REVIEW

PREGNANCY

Ovarian Cancer and Pregnancy

- In the United States, there are approximately 21,400 new cases of ovarian cancer each year (approximately 12% of cases are diagnosed in women less than 45 years). Ovarian cancer is typically diagnosed in advanced stages and standard treatment is surgical staging and cytoreduction followed by adjuvant chemotherapy.[7]
- The incidence of adnexal masses complicating pregnancy ranges from 0.05-2.4%, and approximately 1-6% of these masses are malignant. Approximately half of these malignancies are identified as epithelial ovarian tumors.[8]
- Ovarian cancer is the fifth most common cancer diagnosed during pregnancy. If malignancy is suspected during pregnancy, a laparotomy is performed and if malignancy is confirmed at frozen section, the surgical staging is conducted on an individualized basis depending on the potential risk to the mother and fetus. The

[4] Parenterally administered folate conjugates may reach FRα receptors in proximal tubules of the kidneys but folate conjugates are not retained and toxicity has not been demonstrated. Reference: Low PS, Kularatne SA. Folate-targeted therapeutic and imaging agents for cancer. Curr Opin Chem Biol. 2009 Jun;13(3):256-62.
[5] Applicant's submission Clinical Overview, page 21
[6] Applicant's submission for NDA 214907, Clinical Overview, page 9
[7] https://www.uptodate.com/contents/epithelial-carcinoma-of-the-ovary-fallopian-tube-and-peritoneum
[8] https://www.uptodate.com/contents/adnexal-mass-in-pregnancy

timing of subsequent surgery and chemotherapy is individualized and may also occur after delivery.[9]

Reviewer comment: In discussion with the Clinical team, the majority of patients who receive Cytalux are likely to have stage III or stage IV ovarian cancer. The standard of care is chemotherapy as well as surgery including hysterectomy and salpingo-oophorectomy.

Folate, FRα and Pregnancy

An adequate supply of folate is critical for embryogenesis and normal fetal development. During pregnancy, folate is transported through specific folate transporters in the placenta. (e.g., FRα, the Reduced Folate Carrier, and the Proton Coupled Folate Transporter).[10] Folate deficiency is associated with birth defects (e.g., neural tube defects, cardiac defects, and cleft lip/palate).[11] Folic acid supplementation is recommended for all women of reproductive potential during preconception and the first trimester because it is effective in lowering the risk of neural tube defects.[12] Pafolacianine sodium and folic acid competitively bind to the folate receptor with equal binding affinity.[13]

Reviewer comment: Based on discussions with the review team, while folic acid and pafolacianine sodium competitively bind to FRα, it is unclear whether FRα binding could be overcome with folate supplementation if a pregnant person were exposed to Cytalux.

Nonclinical Experience

The sponsor received a waiver to conduct reproductive toxicology studies from FDA. Reproductive and developmental toxicity studies are limited to embryofetal studies in rats and rabbits.

In initial dose finding embryofetal development studies, there was excessive maternal and embryofetal toxicity. There were no adverse developmental effects observed in rats and rabbits with intravenous administration of pafolacianine during organogenesis (embryofetal development) at doses up to 158-fold (rat) and 570-fold (rabbit) the recommended human dose of 0.025 mg/kg based on AUC, otherwise 9.6- and 38.4-fold based on human equivalent dose (HED) (see Data).

Reviewer comment: While the embryofetal results do not indicate adverse fetal effects at clinically relevant doses, these studies do not fully address the potential adverse effects of pafolacianine binding to FRα with subsequent folate blockade in a developing fetus. Normal FRα

[9] https://www.uptodate.com/contents/adnexal-mass-in-pregnancy
[10] Zhao R, Matherly LH, Goldman ID. Membrane transporters and folate homeostasis: intestinal absorption and transport into systemic compartments and tissues. Expert Rev Mol Med. 2009 Jan 28;11:e4.
[11] Reza-Lopex S. (2018). Folate transporter expression in placenta from pregnancies complicated with birth defects. *Birth Defects Research.*, *110*(16), 1223–1227. https://doi.org/10.1002/bdr2.1356
[12] https://www.uptodate.com/contents/management-of-epilepsy-during-preconception-pregnancy-and-the-postpartum-
[13] Applicant's submission for NDA 214907, Clinical Overview

expression varies between species. [14] *It is not clear to what extent FRα expression in placental tissue differs between rats and rabbits compared to humans or whether rats and rabbits have the same reliance on FRα for folate transfer during pregnancy compared to humans.*

The reader is referred to the full Pharmacology/Toxicology review by Dina Olayinka, PhD, which is currently pending.

Clinical Development Program

In total, more than 615 participants in ten studies have been exposed to pafolacianine sodium injection.[15] Pregnant persons were excluded from clinical trials. There were no inadvertent pregnancies reported during the clinical studies or to the pharmacovigilance database.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in PubMed, Embase, Cochrane Database, and Clinical Trials.gov related to pafolacianine sodium use during pregnancy. Search terms included "pafolacianine," "folate receptor-alpha-targeted fluorescent agent," "OTL0038," "pregnancy," and "pregnant" as well as related search terms. The applicant did not identify any publications.

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex, [16] TERIS, [17] Reprotox, [18] and Briggs[19] to find relevant articles related to the use of pafolacianine sodium during pregnancy. Search terms included "pafolacianine" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss." Pafolacianine was not referenced in Micromedex, TERIS, Reprotox, or Briggs. No relevant articles were identified.

LACTATION

Nonclinical Experience

No animal lactation studies have been performed with pafolacianine.

Review of Pharmacovigilance Database

The applicant did not identify cases of lactation in the pharmacovigilance database.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search in PubMed, Embase, Cochrane Database, and Clinical Trials.gov related to pafolacianine sodium use and lactation. Search terms included

[14] Parker N, Turk MJ, Westrick E, Lewis JD, Low PS, Leamon CP. Folate receptor expression in carcinomas and normal tissues determined by a quantitative radioligand binding assay. Anal Biochem. 2005;338(2):284-93. doi:10.1016/j.ab.2004.12.026

[15] Applicant's submission, Clinical Overview, page 10

[16] https://www.micromedexsolutions.com, accessed 5/17/21

[17] Truven Health Analytics information. Teris, accessed 5/17/21

[18] Truven Health Analytics information. Reprotox, accessed 5/17/21

[19] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 5/17/21

"pafolacianine," "folate receptor-alpha-targeted fluorescent agent," "OTL0038," "lactating" and "breastfeeding" as well as related search terms. The applicant did not identify any publications.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, Micromedex,[20] TERIS, [21] Reprotox, [22] and Briggs, [23] *Medications and Mothers' Milk*,[24] and LactMed[25] to find relevant articles related to the use of pafolacianine during lactation. Search terms included "pafolacianine" AND "breastfeeding" or "lactation." Pafolacianine was not referenced in Micromedex, TERIS, Reprotox, Briggs, *Medications and Mothers' Milk*, or LactMed. No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Genotoxic hazards were not identified when pafolacianine sodium was evaluated in a standard testing battery. Carcinogenicity studies were not conducted. Fertility studies were not conducted.

Review of Pharmacovigilance Database
The applicant did not identify cases of infertility in the pharmacovigilance database.

Review of Literature
Applicant's Review of Literature
The applicant conducted a literature search in PubMed, Embase, Cochrane Database, and Clinical Trials.gov related to pafolacianine sodium and fertility. Search terms included "pafolacianine," "folate receptor-alpha-targeted fluorescent agent," "OTL0038," "fertility" or "sterility" as well as related search terms. The applicant did not identify any publications.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, and Reprotox[26] to find relevant articles related to the use of pafolacianine sodium and effects on fertility. Search terms included "pafolacianine," AND "fertility," "infertility," "contraception," and "oral contraceptives."

DISCUSSION AND CONCLUSIONS
Pregnancy
There are no available human data regarding pafolacianine use in pregnancy in either the pharmacovigilance database or the published literature. Based on the mechanism of action, pafolacianine sodium competitively binds to FRα with equal binding affinity as folic acid. If a pregnant woman were to inadvertently receive Cytalux, it is not known whether this FRα binding is reversible and could be overcome by additional folate supplementation. DPMH discussed with

[20] https://www.micromedexsolutions.com, accessed 5/17/21
[21] Truven Health Analytics information. Teris, accessed 5/17/21
[22] Truven Health Analytics information. Reprotox, accessed 5/17/21
[23] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 5/17/21
[24] https://www.halesmeds.com, accessed 5/17/21
[25] https://www.ncbi.nlm.nih.gov/books/NBK501922/, accessed 5/17/21
[26] Truven Health Analytics information. Reprotox, accessed 5/17/21

Pharmacology/Toxicology and determined that if pafolacianine was administered to a pregnant person, it could bind to FRα in placental tissues and potentially block folate absorption in a developing fetus. Based on the mechanism of action, DPMH and Pharmacology/Toxicology agree with a Warning and Precaution for embryofetal toxicity as well as pregnancy testing prior to Cytalux administration.

Pafolacianine sodium is cleared rapidly from the plasma but remains bound to FRα for a longer duration of time. While pafolacianine sodium could theoretically remain in the body up to five months, the duration the drug remains in the body is unknown. Furthermore, if a woman were to become pregnant after Cytalux administration, even during the period when Cytalux was still bound to FRα in the body, it is not known whether Cytalux would then pose a concern to folate absorption in a developing fetus. Since this patient population predominantly includes females with advanced ovarian cancer who typically receive chemotherapy and surgical intervention including hysterectomy, the likelihood of subsequent pregnancy is low. Based on multiple unknowns in a patient population with low risk of pregnancy, the team decided not to include contraception language.

Since this is a one-time imaging product in a patient population with low likelihood of pregnancy, a pregnancy PMR would likely not be feasible.

Lactation

There are no human or animal data with respect to pafolacianine sodium exposure and lactation. Pafolacianine has a short half-life and high protein biding which suggests minimal potential for drug exposure in the breastfed infant. DPMH recommends subsection 8.2 of labeling for CYALUX contain the risk/benefit statement for lactation. Since this is a one-time imaging product and use of Cytalux during lactation is expected to be rare, a lactation PMR would likely not be feasible.

Females and Males of Reproductive Potential

There are no available animal or human data relevant to fertility. Pafolacianine sodium competitively binds to folate and may potentially interfere with folate absorption in a developing fetus. Since use of pafolacianine sodium is not recommended in pregnancy, DPMH recommends that pregnancy testing and contraception language is added to subsection 8.3 of labeling. Since it is presumed that pafolacianine sodium may remain in the tissue for five months, labeling will recommend that females of reproductive potential use contraception to avoid pregnancy for five months after treatment with Cytalux.

LABELING RECOMMENDATIONS

DPMH revised subsections 2.2, , 5.4, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on June 2, 2021. DPMH recommendations are below and reflect the discussions with DRIM. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

• Embry-fetal Toxicity: CYTALUX may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.4, 8.1, 8.3)

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

(b) (4) Obtain a pregnancy test in females of reproductive potential and verify the absence of pregnancy prior to administration of CYTALUX *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)].*

5 WARNINGS

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, CYTALUX may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to initiating CYTALUX treatment. *[Use in Specific Populations (8.1, 8.3), Clinical Pharmacology 12.1)].].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, CYTALUX may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available human data to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There were no adverse developmental effects observed in rats and rabbits with intravenous administration of pafolacianine during organogenesis (embryofetal development) at doses up to 158-fold (rat) and 570-fold (rabbit) the recommended human dose of 0.025 mg/kg based on AUC, otherwise 9.6- and 38.4-fold based on human equivalent dose (HED) *(see Data).*

The estimated background risks of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2-4% and 15-20% of clinically recognized pregnancies, respectively.

Data

Animal Data

Pafolacianine was administered in intravenous doses of 0, 0.015, 0.15, and 1.5 mg/kg/day (b) (4) (b) (4) to (b) (4) female rats from gestational day (GD)6 until GD17. (b) (4)

8.2 Lactation

Risk Summary

There are no data on the presence of CYTALUX in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CYTALUX and any potential adverse effects on the breastfed infant from CYTALUX or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

CYTALUX may cause fetal harm if administered to a pregnant woman *[see Warnings and Precaution (5.4) and Use in Specific Populations (8.1)]*.

Pregnancy Testing

Obtain a pregnancy test in females of reproductive potential and verify the absence of pregnancy prior to administration of CYTALUX *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

• Advise female of reproductive potential of the potential risk to a fetus and to contact their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*.

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/

JEAN L LIMPERT
06/15/2021 05:02:02 PM

MIRIAM C DINATALE
06/15/2021 05:09:48 PM

LYNNE P YAO
06/17/2021 08:42:57 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 4 June 2021

To: Sharon Thomas, Regulatory Project Manager, (Office of Specialty Medicine/ Division of Imaging and Radiation Medicine)

From: James Dvorsky, Team Leader, Office of Prescription Drug Promotion

CC: David Foss, Regulatory Review Officer, Office of Prescription Drug Promotion

Subject: OPDP Labeling Comments for CYTALUX (pafolacianine sodium injection; OTL38)

NDA/BLA: 214907

In response to the DIRM consult request dated 19 January 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA/BLA submission for Cytalux (pafolacianine sodium injection; OTL38).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received electronically (SharePoint) from DIRM on 3 June 2021 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received electronically (SharePoint) from DIRM on 3 June 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact James Dvorsky at (301) 796-2655 or james.dvorsky@fda.hhs.gov.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

JAMES S DVORSKY
06/04/2021 08:38:26 AM

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:	April 15, 2021
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 214907
Product Name, Dosage Form, and Strength:	Cytalux (pafolacianine sodium) Injection, 3.2 mg/1.6 mL (2 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	On Target Laboratories
FDA Received Date:	December 29, 2020 and January 27, 2021
OSE RCM #:	2020-2754
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

On Target Laboratories submitted 505(b)1 NDA 214907 Cytalux (pafolacianine sodium) injection on December 29, 2020. Cytalux is an optical imaging agent proposed for use in adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant (b) (4) lesions (b) (4). We evaluated the proposed Cytalux prescribing information (PI), vial container label, single vial carton labeling and 10 vial pack carton labeling for 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 1. Materials Considered for this Label and Labeling Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

On Target Laboratories submitted a 505(b)1 application on December 29, 2020 to obtain marketing approval of Cytalux (pafolacianine sodium) injection. We performed a risk assessment of the proposed prescribing information (PI), vial container label, single vial carton labeling, and 10 vial pack carton labeling for Cytalux to determine whether there are deficiencies that may lead to medication errors and other areas of improvement.

Our evaluation of the proposed PI, vial container label, single vial carton labeling, and 10 vial pack carton labeling for Cytalux identified areas of vulnerability that may lead to medication errors. We note inconsistencies exist throughout the proposed prescribing information (PI), vial container label, single vial carton label, and 10 vial pack carton labeling for the storage requirements and dilution information. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Cytalux prescribing information (PI), vial container label, single vial carton labeling, and 10 vial pack carton labeling identified areas of vulnerability that may lead to medication errors. Below, we provide recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to On Target Laboratories so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DMIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. We note the first bullet of the Highlights of Dosage and Administration states [redacted] (b) (4) We recommend removing this bullet from this section as this information is not needed.

b. As currently presented, the second bullet regarding the recommended dose of Cytalux lacks clarity. Additionally, we note that Cytalux will be administered as an intravenous infusion over 60 minutes. We recommend revising the second bullet to read "Recommended dosage is 0.025 mg/kg administered intravenously over 60 minutes".

c [redacted] (b) (4)

d. As currently presented, the fourth bullet states [redacted] (b) (4) We recommend revising this statement to read "See Full Prescribing Information for preparation, administration, and imaging information" in order to include all of the important information covered in Section 2 of the PI.

e. We note the last bullet of the Highlights of Dosage and Administration states [redacted] (b) (4) We recommend removing this bullet as this information is not needed here.

2. Dosage Forms and Strengths

a. We note the dosage form for Cytalux is presented as [redacted]. We recommend removing the word [redacted] and replacing it with the proper Cytalux dosage form, "Injection".

b. We note the use of a trailing zero for the strength. We recommend removing the use of the trailing zero in order to prevent a ten-fold misinterpretation of the strength.

c. As currently presented, the strength in this section is listed as [redacted] We note that Cytalux will be supplied in [redacted], with each vial containing [redacted] We recommend revising to read "Injection: 3.2 mg/1.6 mL (2 mg/mL) of pafolacianine sodium in a single dose vial. (3)".

B. Prescribing Information

1. Section 2: Dosage and Administration

a. We note Section 2.1 is currently titled [redacted] We also note the information provided in Section 2.1 only pertains to the recommended dose. Thus, we recommend revising the title of Section 2.1 to [redacted]

b. As currently presented, Section 2.1 can be revised in order to improve the clarity of important dosing information. Revise Section 2.1 to read "The recommended dosage of Cytalux is 0.025 mg/kg administered intravenously over 60 minutes. Administration must be completed 1 hour to [redacted] hours prior to surgery".

c. We note Section 2.2 is currently titled [redacted] We recommend revising the title of this section to "2.2 [redacted]

d. As currently presented, the first portion of Section 2.2 [redacted]. We recommend removing this section and including a statement in the first portion of Section 2.2 that reads "Use appropriate aseptic technique".

e. We note Section 2 states Cytalux is to be diluted with "5% Dextrose". We recommend presenting this diluent as the USP name, "5% Dextrose Injection, USP" throughout the PI.

f. We note the first paragraph under Section 2.2 provides an introduction to the preparation instructions. We recommend removing this paragraph and only providing the preparation steps in order to improve readability of this section.

g. We recommend including [redacted] as the first step of preparation.

h. As currently presented, the first step under preparation reads "[redacted]". We recommend revising this step to read "Place Cytalux vial at room temperature between [redacted] and 25°C ([redacted] to 77°F) for 90 minutes to thaw".

i. We note the second step under preparation currently states [redacted] We recommend revising this step to remove past tense. Revise to read "Shake the vial or vortex for 60 seconds".

j. As currently presented, the third step under preparation reads "Withdraw the calculated volume for a dose of 0.025 mg/kg [redacted] We recommend dividing this step into three separate steps and revising the language in order to improve readability. We recommend one step read "Withdraw the required volume from the Cytalux vial [redacted] Discard unused portion". For the next step, we recommend it reads [redacted] add into a 250 mL infusion bag of 5% Dextrose Injection, USP". We recommend the third step of this process to read "Gently swirl the bag for 1 minute to mix the solution".

k. We note preparation step 4 currently states [redacted] We recommend revising this step to read [redacted]

l. We note preparation step 5 currently states [redacted], step 6 states [redacted], and step 8 reads [redacted] We recommend combining these three steps into one and having it read "If not immediately used, store the diluted Cytalux solution refrigerated at [redacted] and protect from light for up to 24 hours.".

m. We note [redacted] that no information is provided regarding protecting the prepared solution from light during administration. We recommend including the statement "Protect infusion bag from light during administration" as a part of the fourth bullet.

n. [redacted]

(b) (4)

o. We note in Section 2.2 (b) (4) We recommend revising this bullet to read "Administer by intravenous infusion over 60 minutes using a dedicated infusion line".

p. As currently presented, (b) (4) We recommend revising this bullet to read "Administer Cytalux 1 hour to (b) (4) hours prior to surgery".

q. We note the third and fourth bullets (b) (4) in Section 2.2 provide information regarding proper infusion of Cytalux. We recommend removing the third and fourth bullets as the first and second bullets have been revised to include this information.

r. As currently presented, the title of Section 2.3 is (b) (4) . We recommend revising the title of this section to read "Imaging".

2. Section 3: Dosage Forms and Strengths

a. As currently presented, we note (b) (4) in Section 3. We recommend including the dosage form in the beginning of Section 3 for clarity. Revise the first line of Section 3 to read "Injecton: 3.2 mg/1.6 mL (2 mg/mL) pafolacianine sodium in a single dose vial".

b. We note in Section 3 the Cytalux vial is described as (b) (4) Additionally, we note that Cytalux will be supplied in single-dose vials. Thus, we recommend removing (b) (4) and defining the package type as "single dose vial".

c. We note Section 3: Dosage Forms and Strengths (b) (4) . We recommend including a physical description of the solution in this section.

3. Section 16: How Supplied/Storage and Handling

a. We recommend including subheadings in Section 16 in order to improve the readability of this section. We recommend including one subheading for "How Supplied" and one subheading for "Storage and Handling".

b. We note in Section 16 under How Supplied (b) (4) We recommend including a physical description of Cytalux in Section 16 underneath the How Supplied section.

c. We note Section 16 under How Supplied the Cytalux vial is described as (b) (4) Additionally, we note that Cytalux will be supplied in

single-dose vials. Thus, we recommend removing [redacted] (b) (4) and defining the package type as "single dose vial".

d. We recommend revising the 'How Supplied' statement in order to improve the readability. We recommend revising the statement to read "Cytalux is a solution available in single dose vials of 3.2 mg/1.6 mL (2 mg/mL) in a carton of 10 vials (NDC 81052-138-10).".

e. As currently presented, the storage information is presented as [redacted] (b) (4) in order to prevent confusion. Additionally, we recommend including the allowed range as [redacted] (b) (4) and including the Fahrenheit equivalent temperature presented in parenthesis after each Celsius temperature. Revise the storage temperature statement to read "Store frozen at [redacted] (b) (4). Store in original carton to protect from light. [redacted] (b) (4)

4.2 RECOMMENDATIONS FOR ON TARGET LABORATORIES

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

A. Vial Container Label

1. Consider revising the statement [redacted] (b) (4) to read "Single-Dose Vial. Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.
2. As currently presented, the strength of Cytalux is displayed on the vial container label as "3.2 mg / 1.6 mL (2 mg/mL)". We note the presence of extra spaces before and after the "/" symbol. We recommend removing those extra spaces to increase readability. In addition, we note the strength per milliliter, "(2 mg/mL)", presented immediately after the overall strength in the same font size on the vial container label. We recommend utilizing a smaller font for the strength per milliliter on the vial container label in order to avoid confusion. Revise to "3.2 mg/1.6 mL (2 mg/mL)".
3. We note the net quantity is not present on the container label. Per 21 CFR 201.51 the net quantity statement (i.e. 1.6 mL) should appear on the principal display panel. Ensure the net quantity statement is away from the product strength, such as the bottom of the principal display panel.

B. 10 Vial Pack Carton Labeling

1. We recommend placing the net quantity statement at the bottom of the principal display panel. In addition, consider revising the statement "10 x 1.6 mL Single-Dose Vials" to read "10 x 1.6 mL Single-Dose Vials. Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.
2. We recommend increasing the prominence of the route of administration to prevent this important information from being missed.
3. As currently presented, the storage information is presented on multiple panels. Remove the storage information from the principal display panel. In addition, place the "protect from light" statement next to the rest of the storage information. We recommend revising this storage statement for clarity to read "Store in freezer at (b) (4) -25°C to -15°C (-13°F to 5°F). Store in original carton to protect from light. Thaw at room temperature at (b) (4) to 25°C ((b) (4) to 77°F) for 90 minutes in the carton prior to (b) (4) preparation.".
4. As currently presented, the side panel states (b) (4) We recommend revising these statements to read "Recommended Dosage: See Prescribing Information.".
5. We note the expiration date format is not identified. 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 slash or a hyphen be used to separate the portions of the expiration date.

C. Single Vial Carton Labeling

1. We recommend increasing the prominence of the route of administration to prevent this important information from being missed.
2. We recommend placing the net quantity statement at the bottom of the principal display panel. In addition, consider revising the statement (b) (4) to read "1 Single-Dose Vial. Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.
3. As currently presented, the storage information is presented on multiple panels. Remove the storage information from the principal display panel. In addition, place the "protect from light" statement next to the rest of the storage information. We recommend revising this storage statement for clarity to read "Store in freezer at (b) (4) -25°C to -15°C (-13°F

to 5°F). Store in original carton to protect from light. Thaw at room temperature at (b) (4) to 25°C ((b) (4) to 77°F) for 90 minutes in the carton prior to (b) (4) preparation.”.

4. As currently presented, the side panel states (b) (4) We recommend revising these statements to read “Recommended Dosage: See Prescribing Information.”.

5. We note the proposed single vial carton labeling does not contain a placeholder for the lot number and the expiration date. We recommend including the lot number and the expiration date on the single vial carton labeling. 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 slash or a hyphen be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cytalux received on December 29, 2020 from On Target Laboratories.

Table 2. Relevant Product Information for Cytalux	
Initial Approval Date	N/A
Active Ingredient	pafolacianine sodium
Indication	Cytalux is an optical imaging agent indicated for adult patients with known or suspected ovarian cancer as an adjunct for intraoperative identification of malignant (b) (4) lesions (b) (4)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	3.2 mg/1.6 mL (2 mg/mL)
Dose and Frequency	0.025 mg/kg administered intravenously 1 hour to (b) (4) hours prior to surgery.
How Supplied	Cytalux (pafolacianine sodium) is provided in (b) (4) amber vials. Each vial contains 3.2 mg pafolacianine sodium in 1.6 mL of sterile solution (2 mg/mL), 14.4 mg sodium chloride, 0.23 mg potassium phosphate monobasic, 1.27 mg sodium phosphate dibasic heptahydrate and adjusted for pH with sodium hydroxide or hydrochloric acid. Cytalux is supplied as 1.6 mL frozen solution containing 3.2 mg active drug in a (b) (4), 3 mL amber vial, packaged as a 10-vial carton.
Storage	Store at -20°C (+/-5°) and protect from light.

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,[a] along with postmarket medication error data, we reviewed the following Cytalux labels and labeling submitted by On Target Laboratories.

- Vial Container label received on December 29, 2020
- Single Vial Carton labeling received on December 29, 2020
- 10 Vial Pack Carton Labeling received on December 29, 2020
- Prescribing Information (Image not shown) received on December 29, 2020, available from \\CDSESUB1\evsprod\nda214907\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-pdf.pdf

G.2 Label and Labeling Images

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DEVIN R KANE
04/15/2021 02:54:10 PM

HINA S MEHTA
04/16/2021 02:49:32 PM