CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216755Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 19, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216755
Product Name, Dosage Form, and Strength:	Likmez (metronidazole) Oral Suspension, 500 mg/5 mL
Applicant/Sponsor Name:	Saptalis Pharmaceuticals, LLC (Saptalis)
TTT ID #:	2022-2881-3
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on September 15, 2023 for Likmez. The Division of Anti-Infectives (DAI) requested that we review the revised container label for Likmez (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous label and labeling review.[a]

2 CONCLUSION

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

[a] Myers, D. Label and Labeling Review Memo for Likmez (NDA 216755). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2. TTT ID No.: 2022-2881-2.

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

---

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/

DEBORAH E MYERS
09/19/2023 10:05:28 AM

VALERIE S VAUGHAN
09/19/2023 10:08:33 AM

M E M O R A N D U M

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

DATE: August 24, 2023

TO: Partha Roy, Ph.D.
Director
Office of Bioequivalence
Office of Generic Drugs

Peter Kim, M.D.
Director
Division of Anti-Infectives
Office of Infectious Diseases
Office of New Drugs

FROM: Kimberly A. Benson, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of For-Cause Clinical Inspection of Veeda Clinical Research Pvt. Ltd., Mehsana, Gujarat, India

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a for-cause inspection of the clinical portions of studies NON-RESPONSIVE NON-RESPONSIVE and 21-VIN-0347 (NDA 216755/IND 132217) conducted at Veeda Clinical Research Pvt. Ltd., Mehsana, Gujarat, India. In addition, during the inspection of this site, the presence of reserve samples for studies NON-RESPONSIVE NON-RESPONSIVE was confirmed.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. Four discussion items were raised with the site at the close-out of the inspection. Based on the inspection findings, there are no identified concerns for Veeda Clinical Research Pvt. Ltd., regarding reliability of the data or human subject protection for inspected studies NON-RESPONSIVE and 21-VIN-0347 (NDA 216755) for the review division consideration. Additionally, there were no concerns over the reserve samples for study NON-RESPONSIVE

NON-RESPONSIVE. There were, however, fewer remaining drug products of both the test product and the reference product for studies NON-RESPONSIVE than required by 21 CFR 320.38 and the recommendation of 30 capsules from "*Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c) Guidance for Industry*" (August 2020). Based on the information in **Attachment 1** and **Attachment 2**, these remaining drug products are representative of the test and reference products used in studies NON-RESPONSIVE. I recommend the remaining test and reference products from NON-RESPONSIVE, and NON-RESPONSIVE be accepted as reserve samples.

The current inspection was for cause related to a whistle-blower complaint received by the EMA alleging under-reporting of SAEs, negligence, and falsification of data. The ORA investigators did not note any concerns with SAE reporting, nor did they identify any signs of negligence or falsification of data in the audited studies.

2. Inspected Studies:

NON-RESPONSIVE

NDA 216755/IND 132217

Study Number: **21-VIN-0347**
Study Title: "An open label, balanced, randomized, single-dose, two-treatment, two sequence, two period, crossover oral comparative bioavailability study of Metronidazole Oral Suspension 500 mg / 5 mL of Saptalis Pharmaceuticals, LLC., 45 Davids Drive, Hauppauge, NY 11788 and Metronidazole Tablets USP 500 mg of Teva Pharmaceuticals USA, Inc., North Wales, PA 19454 in Healthy, Adult, Human Subjects under Fasting Conditions"

Dates of Conduct: 02/15/2022 – 02/27/2022
Principal Investigator: Dr. Axay Parth

NON-RESPONSIVE

Clinical site: Veeda Clinical Research Limited, Office no. 9, 10 & 11- 1st, 2nd and 3rd Floor, Radhe Palladium, Panchot, Mehsana, Gujarat 384205, India

3. Inspectional Findings

Veeda Clinical Research Pvt. Ltd., Mehsana, Gujarat, India

ORA investigators Tawny L. Colling and Habacuc V. Barrera inspected Veeda Clinical Research Pvt. Ltd., Office no. 9, 10 & 11- 1st, 2nd and 3rd Floor, Radhe Palladium, Panchot, Mehsana, Gujarat, India from May 15-19, 2023.

3.1 Previous Inspection(s)

The previous OSIS inspection of Veeda Clinical Research Pvt. Ltd was conducted August 23-27, 2021. At the conclusion of the inspection, a one-item Form FDA 483 was issued for failing to obtain the x-ray source images from the third-party vendors. There were three discussion items. These addressed (1) potential for identification cards to be manipulated by subjects, (2) duration of time documented for vital signs, physical exams, and adverse events appeared to be uniform for most subjects, and (3) drug storage documentation. The final classification was VAI.

During the current inspection, Investigator Colling confirmed that the firm had access to all the x-ray films for subjects randomized into the inspected study. The EIR did not confirm any corrective actions for the discussion items, however, similar findings were not included in the 2023 EIRs.

3.2 Current Inspection

The current inspection included auditing the following items:

Studies NON-RESPONSIVE **and 21-VIN-0347(NDA 216755/IND 132217)**

- Subject records
- Informed consent forms
- Protocol deviations
- Independent ethics committee approvals
- Training records
- Randomization and dosing
- Concomitant medication
- Adverse events
- Reserve samples

Studies NON-RESPONSIVE

- Reserve samples

3.3 Inspection finding(s)

At the conclusion of the inspection, Investigators Tawny L. Colling and Habacuc V. Barrera Rebecca Davis did not observe any

objectionable conditions and did not issue Form FDA 483 to the clinical site. There were four items discussed with the site at the completion of the inspection.

3.3.1 FDA 483 Observations

None

3.3.2. Discussion Items (if applicable)

Discussion item 1: As a general practice at Veeda, subjects sign a screening ICF, then later a study specific ICF once they've met all inclusion criteria. The site was told by the ORA investigators that subjects can still sign the study specific consent without all eligibility results, they just cannot be dosed without them.

OSIS Evaluation: This discussion item speaks to the timing of, and time it takes to, screen subjects and sign the study specific consent form. The ORA investigators discussed this with the site to ensure that they understood that they did not need to wait for all eligibility criteria results before having a subject sign the study-specific consent; they just cannot dose the subjects until the results were all received, and eligibility determined. This does not, however, impact the reliability of the data or the subject safety from the audited studies.

Firm's Response: The site did not have any disagreements with the discussion items. Dr. Vadhvana, Head of Clinical Research, stated that they will make sure screening procedures are done with sufficient time to ensure subjects aren't signing study ICF late into the night.

Discussion item 2: As a general practice at Veeda, "impartial witnesses" are provided to illiterate subjects; however, these witnesses are paid by the site on an on-call basis. Because these individuals are paid by the site, this takes away the impartiality of it and allows for the potential to be biased.

OSIS Evaluation: This discussion item is not specific to the audited studies but one related to a general practice of the site, a practice that they intend to discontinue. There is no regulation that prohibits a site from paying the witnesses. This discussion item does not impact the data reliability of the audited studies.

Firm's Response: The site did not have any disagreements with the discussion items. Dr. Vadhvana stated that they were no longer going to include illiterate subjects within their healthy subject populations or subjects need to bring someone to act as a witness for them.

Discussion item 3: Despite subjects having varying degrees of educational levels from second grade onward, all ICF versions were the same and not written at a level that everyone could fully understand.

OSIS Evaluation: There is no regulation that requires the ICF to be presented in differing reading comprehension levels. The EIR did not provide any evidence that suggests the study subjects may not have fully understood the ICF for the audited studies. This discussion item does not impact the data reliability or subject safety.

Firm's Response: The site did not have any disagreements with the discussion items. The site stated that they explain the study to subjects in a level of understanding that they can grasp.

Discussion item 4: The site did not follow their SOPs regarding documenting visitors; visitors were documented in both a handwritten logbook and electronically. When the visitor logs from February 2022 were requested, the site immediately looked in the paper logbooks and had difficulty finding specific visitors during that month. Later the site found them in the electronic logbook. Their SOP states that volunteers are to be logged electronically, utilizing the paper books only if the system is down. Security appeared to be logging visitors in either the paper or electronic logbooks, regardless of whether the electronic system was working or not.

OSIS Evaluation: Following their own SOP would ensure consistent documentation of the visitors to the site. By visitors, the ORA investigators are referring to visitors to the site such as maintenance workers, contractors, cleaners (per a discussion with Investigator Colling). The site prohibits visitors for study subjects during the trial. Future inspections of this site should ensure that they are consistently following the SOP. This discussion item does not impact the data reliability or subject safety.

Firm's Response: The site did not have any disagreements with the discussion items.

3.3.3. Specific concerns from OGD

OGD notified OSIS regarding the potential to verify the status of any remaining drug from three studies that were initially designated as pilot studies. The sponsor wishes to use these studies as pivotal studies and would like the remaining drug products to serve as reserve samples. This issue is related to ANDA NON-RESPONSIVE, hence the inclusion of studies NON-RESPONSIVE NON-RESPONSIVE in this inspection. The investigators were asked only to confirm the presence of reserve samples for these studies. The investigators confirmed that the site retained the appropriate amount of reserve samples and stored them in the appropriate conditions for study NON-RESPONSIVE. The same confirmation was done for studies NON-RESPONSIVE and 21-VIN-0347 (NDA 216755/IND 132217).

However, for studies NON-RESPONSIVE the site had less than 30 capsules, (per the August 2020 Guidance for Industry) of the remaining drug products. Upon completion of the studies, the sponsor decided to submit them as pivotal studies. Two formulations of test product were used, with each formulation used in both studies NON-RESPONSIVE. All of the test product capsules were received by the site in the same shipment on November 19, 2021, as seen in **Attachment 1; pages 2-3**. One lot of the reference product was also received on November 19, 2021 (**Attachment 1; page 4**).

Photographs of all the reserve samples or remaining drug products under ANDA NON-RESPONSIVE, as well as those from studies NON-RESPONSIVE NON-RESPONSIVE and 21-VIN-0347 (NDA 216755), are seen in **Attachments 2 and 3**. The inspection verified that the remaining drug products from NON-RESPONSIVE are representative of the test and reference products used in these studies and they were stored under appropriate conditions (per email discussions with the ORA investigator). I recommend that these remaining drug products may serve as the reserve samples for studies NON-RESPONSIVE.

Attachment(s)

Attachment 1: IP accountability records; Sponsor's letter to FDA requesting acceptance of pilot study

Attachment 2: Photographs of reserve samples for NON-RESPONSIVE NON-RESPONSIVE

Attachment 3: Photographs of reserve samples for 21-VIN-0347 (NDA 216755)

Kimberly A. Benson, Ph.D.
Deputy Division Director

Draft: KAB 08/14/2023; 8/15/2023/ 8/16/2023/ 8/17/2023/ 8/18/2023/ 8/21/2023; 8/22/2023
Edit: SA 08/15/2023, 8/17/23, 8/18/23, 8/21/23, 8/23/23; JC 8/18/2023XX, 8/21/23, 8/22/23, 8/23/23

File #: BE (b) (4) (NDA 216755), BE (b) (4) (ANDA NON-RESPONSIVE) and BE (b) (4) (ANDA NON-RESPONSIVE)

eNSpect Assign D: (b) (4)
eNSpect OpID: (b) (4)

_____
Kimberly Benson, Phd

_____
Stanley Au, PharmD

_____
Seongeun (Julia) Cho, Phd

60 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

KIMBERLY A BENSON
08/30/2023 10:50:12 AM

STANLEY AU
08/30/2023 11:37:01 AM
Secondary reviewer

SEONGEUN CHO
08/30/2023 12:03:02 PM

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

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

Memorandum

Date: August 22, 2023

To: Shraddha Pandey, Clinical Reviewer
Division of Anti-Infectives Products (DAIP)

Sheel Shah, Regulatory Project Manager, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for LIKMEZ™ (metronidazole) oral suspension

NDA: NDA 216755

In response to DAIP's consult request dated August 4, 2023, OPDP has reviewed the proposed product labeling (PI) and Patient Package Insert (PPI) for the original NDA submission for LIKMEZ™ (metronidazole) oral suspension.

PI/PPI: OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 11, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on August 21, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on June 28, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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

---

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/

LATOYA S TOOMBS
08/22/2023 01:58:54 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 21, 2023
To:	Sheel K. Shah, PharmD, RPh Regulatory Project Manager **Division of Anti-Infectives (DAI)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Sheneé Toombs, PharmD, CPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LIKMEZ (metronidazole)
Dosage Form and Route:	oral suspension
Application Type/Number:	NDA 216755
Applicant:	Saptalis Pharmaceuticals, LLC

1 INTRODUCTION

On November 22, 2022, Saptalis Pharmaceuticals, LLC submitted for the Agency's review an original New Drug Application (NDA) 216755 for LIKMEZ (metronidazole) oral suspension. LIKMEZ (metronidazole) oral suspension is a nitroimidazole antimicrobial with a proposed indication to treat the following:

- Trichomoniasis in adults
- Amebiasis in adults and pediatric patients
- Anaerobic Bacterial Infections in adults

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on August 4, 2023, for DMPP and OPDP to review the Applicant's proposed PPI for LIKMEZ (metronidazole) oral suspension.

2 MATERIAL REVIEWED

- Draft LIKMEZ (metronidazole) oral suspension PPI received on November 22, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on August 11, 2023.
- Draft LIKMEZ (metronidazole) oral suspension PPI received on November 22, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on August 11, 2023.
- Draft LIKMEZ (metronidazole) oral suspension Prescribing Information (PI) received on November 22, 2022, revised by the review division throughout the review cycle, and received by DMPP on August 11, 2023.
- Draft LIKMEZ (metronidazole) oral suspension Prescribing Information (PI) received on November 22, 2022, revised by the review division throughout the review cycle, and received by OPDP on August 11, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

---

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/

NYEDRA W BOOKER
08/21/2023 08:42:35 AM

LATOYA S TOOMBS
08/21/2023 01:31:39 PM

LASHAWN M GRIFFITHS
08/21/2023 01:45:11 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 7, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216755
Product Name, Dosage Form, and Strength:	Likmez (metronidazole) Oral Suspension, 500 mg/5 mL
Applicant Name:	Saptalis Pharmaceuticals, LLC (Saptalis)
TTT ID #:	2022-2881-2
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

This memorandum captures an additional container label recommendation based on new information received from our Office of Pharmaceutical Quality (OPQ) colleagues about the storage of Likmez. The Division of Anti-Infectives (DAI) requested that we review and provide any necessary recommendations for the container label for Likmez (Appendix A) to minimize the risk of medication errors.

2 DISCUSSION & CONCLUSION

DMEPA previously reviewed the proposed prescribing information and container label[a], finding the revised container label acceptable from a medication error perspective (Appendix A).[b]

Subsequently, the OPQ determined that the proposed product is only stable for 10 days after the container is opened. Thus, the Agency recommends adding the statement "Discard 10 days after opening container" to the PI, Section 16 *How Supplied/Storage and Handling*, *Storage*.

[a] Myers, D. Label and Labeling Review for Likmez (NDA 216755). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 06. TTT ID No.: 2022-2881.

[b] Myers, D. Label and Labeling Review Memorandum for Likmez (NDA 216755). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUL 05. TTT ID No.: 2022-2881-1.

Considering that it has been determined that the product has a different expiration date after opening, from a medication error perspective, we determined the container label should have a designated space and format for end-users to write the beyond-use date to minimize the risk of deteriorated drug medication errors.

Thus, given the above concern, we provide the identified medication error issue, our rationale for concern, and our proposed recommendation to minimize the risk for medication error in Section 3, for Casper Pharma LLC.

3 RECOMMENDATIONS FOR SAPTALIS PHARMACEUTICALS, LLC (SAPTALIS)

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

Table 1. Identified Issues and Recommendations for Saptalis (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	We note that the proposed product is stable for 10 days after the container is opened. Thus, the Agency recommends adding the statement "Discard 10 days after opening container" to the prescribing information (PI), Section 16 *How Supplied/Storage and Handling*, *Storage*. However, as currently presented, there is no space for end-users to write the beyond-use date, which is the date and time the opened product must be discarded.	Since the product has a different expiration date after opening, the container label should have a designated space and format for end-users to write the beyond-use date to minimize the risk of deteriorated drug medication errors.	We recommend including a space for end-users to write the beyond-use date on the container label. For example: Discard after ___/____/____ Time_____ In addition, consider using a different color font, boxing, and/or highlighting the information to draw attention to this important information.

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

---

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/

DEBORAH E MYERS
08/07/2023 09:23:13 AM

VALERIE S VAUGHAN
08/07/2023 09:35:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Memorandum

Date: 7/21/23 **Date Consulted:** 12/29/22

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., M.S., Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Sheel Shah, Regulatory Product Manager (RPM)
Division of Anti-infectives (DAI)

Drug: Likmez (metronidazole oral suspension)

NDA: NDA 216755

Indication: Treatment of symptomatic Trichomoniasis, asymptomatic Trichomoniasis, asymptomatic sexual partners, Amebiasis and bacterial infections

Applicant: Saptalis Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation labeling [new 505(b)(2) New Drug Application (NDA), Pregnancy and Lactation Labeling Rule (PLLR) Language]

Materials Reviewed:

- Applicant's background package for NDA 216755, submitted on 11/23/22.
- An information request (IR), dated 1/9/23, was sent to the applicant requesting PLLR supporting information.
- Applicant's revised labeling, literature review and summary of pharmacovigilance database submitted on 2/1/23.
- DPMH consult review of NDA 018890/S-055 Metronidazole Injection, USP, 500 mg (5 mg/mL), NDA 012623/S-070 FLAGYL (metronidazole) Tablets, NDA 020334/S-013 FLAGYL® (metronidazole) Capsules, NDA 020868/S-015 FLAGYL® ER

(metronidazole) Extended-Release Tablets. Katherine Kratz, M. D. 3/22/2023. DARRTS Reference ID # 5146007[1].

- NON-RESPONSIVE
- DPMH PLLR review of Vandazole (metronidazole vaginal gel 0.75%) NDA 21806. Christos Mastroyannis, M.D., dated December 22, 2020. DARRTS Reference ID # 4721588[3].
- DPMH PLLR review of NDA 21789 MetroGel 1% (metronidazole gel). Jane Liedtka, M.D, 3/25/19. DARRTS Reference ID # 4406084[4].
- DPMH consult review of Solosec[5] (secnidazole), NDA 209363. Jane Liedtka, M.D. 8/25/17. DARRTS Reference ID 4143279.
- DPMH consult review of Pylera[6] (bismuth subcitrate, metronidazole, tetracycline) NDA 50786, S-012. Tamara Johnson, M.D. February 9, 2018, DARRTS Reference ID 4219957.
- Pediatrics and Maternal Health Staff (PMHS) review of Pylera (bismuth subcitrate, metronidazole, tetracycline) NDA 50786 S-003. Jeanine Best, MSN, RN, PNP. 11/16/10. DARRTS Reference ID: 2864248[7].

Consult Question: Please review the relevant sections of labeling for LIKMEZ and the listed drug (LD) and provide your input on the Applicant's proposed changes.

Please evaluate whether the proposed LIKMEZ labeling contains all of the required sections in PLLR format. For example, we note that section 8.3 Females and Male Reproductive Potential is missing.

INTRODUCTION AND BACKGROUND

DPMH has conducted multiple reviews for metronidazole,[1-7] the most recent of which was finalized on 3/22/2023[1] (see above). Please refer to previous DPMH reviews of

[1]DPMH consult review of NDA 018890/S-055 Metronidazole Injection, USP, 500 mg (5 mg/mL), NDA 012623/S-070 FLAGYL® (metronidazole) Tablets, NDA 020334/S-013 FLAGYL® (metronidazole) Capsules, NDA 020868/S-015 FLAGYL® ER (metronidazole) Extended-Release Tablets. Katherine Kratz, M. D. 3/22/2023. DARRTS Reference ID # 5146007.

[2] NON-RESPONSIVE

[3] DPMH PLLR review of Vandazole (metronidazole vaginal gel 0.75%) NDA 21806. Christos Mastroyannis, M.D., dated December 22, 2020. DARRTS Reference ID # 4721588.

[4]DPMH PLLR review of NDA 21789 MetroGel 1% (metronidazole gel). Jane Liedtka, M.D, 3/25/19. DARRTS Reference ID # 4406084.

[5]DPMH consult review of Solosec1 (secnidazole), NDA 209363. Jane Liedtka, M.D. 8/25/17. DARRTS Reference ID 4143279.

[6] DPMH consult review of Pylera (bismuth subcitrate, metronidazole, tetracycline) NDA 50786, S-012. Tamara Johnson, M.D. 2/9/18, DARRTS Reference ID # 4219957.

[7] Pediatrics and Maternal Health Staff (PMHS) review of Pylera (bismuth subcitrate, metronidazole, tetracycline) NDA 50786 S-003. Jeanine Best, MSN, RN, PNP. 11/16/10. DARRTS Reference ID: 2864248.

metronidazole for Drug Characteristics, Current State of Labeling, Nonclinical Experience, and Review of the literature.

On 12/29/22, DAI consulted DPMH to provide input regarding the appropriate format and content of Likmez (metronidazole oral suspension) labeling to be in compliance with PLLR.

- Likmez (metronidazole oral suspension), NDA 216755, is a nitroimidazole antimicrobial. The moiety metronidazole was first approved in the US in 1963 as a tablet, Flagyl (metronidazole) and was approved by FDA under NDA 012623.
- On 11/23/22, the applicant submitted a new 505(b)(2) New Drug Application (NDA), NDA 216755, for a metronidazole suspension indicated for treatment of symptomatic Trichomoniasis, asymptomatic Trichomoniasis, asymptomatic sexual partners, Amebiasis and bacterial infections. The "listed drug" for this application is Flagyl (metronidazole) tablets, (NDA 012623), holder - Pfizer Inc.
- On 1/9/23, the Agency requested information to support the Pregnancy and Lactation labeling subsections for this product.
- On 2/1/23, the Applicant submitted revised labeling, literature review and a summary of the pharmacovigilance database regarding the use of metronidazole in pregnant and lactating women.
- Metronidazole is also available as a topical cream, a topical gel, a vaginal gel, an oral tablet, an extended-release oral tablet, an oral capsule and as a parenteral solution for injection. Indications include rosacea for the topical gel and cream, numerous bacterial and protozoal infections for the systemic formulations and trichomoniasis and bacterial vaginosis for the vaginal gel.

REVIEW

History of Pediatric and Maternal Health Staff (PMHS) and DPMH Reviews

Currently approved labeling for metronidazole use during pregnancy is inconsistent across multiple ANDAs, 505(b)(2) NDAs and the original innovator Flagyl, with some including contraindications to use in the first trimester of pregnancy and others lacking this contraindication. The majority of labeling for systemic formulations under subsection 8.1 Pregnancy includes the following language:

> There are no adequate and well-controlled studies with the use of Flagyl in pregnant women. There are published data from case-control studies, cohort studies, and 2-meta-analyses that include more than 5000 pregnant women who used metronidazole during pregnancy. Many studies included first trimester exposures. One study showed an increased risk of cleft lip, with or without cleft palate, in infants exposed to metronidazole in-utero; however, these findings were not confirmed. In addition, more than ten randomized placebo-controlled clinical trials enrolled more than 5000 pregnant women to assess the use of antibiotic treatment (including metronidazole) for bacterial vaginosis on the incidence of preterm delivery. Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy. Three studies conducted to assess the risk of infant cancer following metronidazole exposure during

> pregnancy did not show an increased risk; however, the ability of these studies to detect such a signal was limited.

Multiple reviews by the Division of Pediatrics and Maternal Health (DPMH) have been performed for the moiety metronidazole. The first review (Best[7] -2010) resulted in the inclusion of the above labeling language and also included the following quotes from additional pregnancy recommendation sources:

> REPROTOX[8] ® summarizes metronidazole reproductive risk as follows: "Metronidazole use during pregnancy has not been shown to increase the risk of adverse pregnancy outcome."

> TERIS[9]® summarizes metronidazole reproductive risk as follows: "Magnitude of teratogenic risk to a child born after exposure during gestation is none to minimal. Quality and quantity of data on which risk estimate is based is good."

The 2010 review concluded with the following recommendation regarding metronidazole labeling for pregnancy:

> Metronidazole is currently classified as a pregnancy category B drug, which is still an appropriate classification given the available human and animal data. [Maternal Health Team] notes the current approved Flagyl (metronidazole) labeling contains inconsistent and outdated pregnancy use information. Flagyl is classified as a pregnancy category B drug product based on no human data and negative animal data regarding teratogenicity; however, labeling also contains a contraindication for first trimester treatment of trichomoniasis because of a lack of human data and information from animal studies that the drug transfers across the placental. Flagyl and all metronidazole labeling should be revised to reflect published human data.

In 2019, a subsequent metronidazole review (Liedtka[4] -2019) included similar recommendations to standardize and revise the pregnancy labeling for metronidazole products and included multiple publication citations supporting this recommendation (See Attachment B for Tables from that review). The Discussion and Conclusion Section from the 2019 review noted,

> There are extensive pregnancy outcome data available on the use of metronidazole during pregnancy. The majority of the publications in the literature report no increase in adverse pregnancy outcomes. There are some reports of an increase in specific congenital malformations such as oral cleft (2 studies) or polysyndactyly (one study) but these were not confirmed in numerous additional studies. Two studies reported an increase in spontaneous

[8] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 1/3/19.
[9] DPMH PLLR review of NDA 21789 MetroGel 1% (metronidazole gel) by Jane Liedtka, M.D, dated March 25, 2019. DARRTS Reference ID 4406084.

> abortion (SAB) and one study reported an increase in low birth weight but again, these findings were not confirmed in multiple additional studies. The genotoxicity findings will be included in the Warnings section of labeling and Section 8 will provide a summary of what information is available.

Additional DPMH reviews were conducted for metronidazole in 2020 (Mastroyannis -2020) and 2022 (Mastroyannis -2022) which cited many of the same publications as the 2019 review. None of the DPMH reviews concerning the use of metronidazole during pregnancy recommended a contraindication for any trimester of pregnancy. Instead, based on a summary of the extensive literature, all the DPMH reviews came to the conclusion that evidence from human trials did not support an increased incidence of adverse pregnancy outcomes. The rare earlier reports of such associations were not confirmed by later studies, with more modern design, which controlled for a larger number of confounding factors.

With regard to use of metronidazole during lactation, a comprehensive review was conducted and archived in DARRTS on 3/22/23 (Kratz[1]-2023). This report reviews the literature and recommends removal of the warning for tumorigenicity from the Nursing Mother's section of Flagyl labeling based on the following

> In terms of tumorigenicity, these nonclinical findings were related to chronic administration of metronidazole to mice and rats rather than acute administration as would be the case for these Flagyl products in which the usual duration of therapy is up to 10 days. Additionally, no human studies have found a relationship between metronidazole and tumorigenicity. Flagyl is approved to treat amebiasis in children, and per the DPMH-Pediatrics Team, Flagyl is used extensively in pediatric patients for many conditions, including anerobic infections, Giardia, and Clostridium difficile.

Applicant's Review of Literature

The applicant performed a literature search using the terms 'metronidazole" and "pregnancy" or "lactating women" in PubMed, FDA.gov, and ClinicalTrials.gov databases encompassing the period between 1/1/1995 through 1/24/2023. The applicant identified 16 publications. See Attachment A for a table of these 16 publications. Many of these did overlap with the search performed by DPMH for past reviews. See previous metronidazole reviews for details of DPMH's Review of Literature and analyses. See Attachment B for tables reproduced from previous DPMH reviews and publications cited by DPMH reviews.

See DPMH's recent review[1] by Katherine Kratz, M. D., dated 3/22/2023, comprehensively reviews the subject of metronidazole and lactation.

Females and Males of Reproductive Potential

No formal fertility studies in humans have been reported with metronidazole. A single article was found discussing metronidazole and human fertility and did not find any negative effects. Pregnancy testing and contraception are not recommended by DPMH for metronidazole. DPMH recommends omitting subsection 8.3 from labeling for metronidazole.

DISCUSSION AND CONCLUSIONS

At the time of this memorandum, DPMH recommends removal of the contraindication for use of metronidazole during the first trimester of pregnancy from all metronidazole product labeling. In addition, DPMH recommends removal of the warning for tumorigenicity from the Nursing Mother's/Lactation subsection of all metronidazole product labeling for acute or short term duration.

Given the relatively large amount of currently available literature regarding the use of metronidazole during pregnancy, DPMH does not recommend any post-marketing pregnancy safety studies at this time for this product. There is already information available regarding metronidazole's presence in human milk, so no post-marketing lactation studies are recommended at this time for this product.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of metronidazole labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DAI on 6/20/2023. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Likmez (metronidazole oral suspension) Pregnancy and Lactation Labeling

(b) (4)

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

Attachment A

Table 1: Review and summary of all available published literature regarding metronidazole (in all formulations) use in pregnant and lactating women and the effects of metronidazole on male and female fertility

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
Aliabadi et al., 2022	Antibiotic use in endodontic treatment during pregnancy: A narrative review	NA (Review Article)	Pregnant women	NA	NA	Using antibiotics during pregnancy are allowed, and they can be used normally and safely by pregnant women.
Brocklehurst et al., 2013	Antibiotics for treating bacterial vaginosis in pregnancy	NA (Review Article)	Pregnant Women	7847	NA	Antibiotic treatment can eradicate bacterial vaginosis in pregnancy. The overall risk of Pre-term Birth (PTB) was not significantly reduced. This review provides little evidence that screening and treating all pregnant women with bacterial vaginosis will prevent PTB and its consequences. When screening criteria were broadened to include women with abnormal flora there was a 47% reduction in preterm birth, however this is limited to two included studies.

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
Carey et al., 2000	Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis (BV)	1:1 Randomized double blind – metronidazole capsule or lactose placebo	Pregnant Women	1953 (966 women assigned to metronidazole group and 987 in placebo group)	48 hours 2 g/dose	The treatment of asymptomatic bacterial vaginosis in pregnant women does not reduce the occurrence of preterm delivery or other adverse perinatal outcomes
Haahr et al., 2016	Treatment of bacterial vaginosis in pregnancy in order to reduce the risk of spontaneous preterm delivery – a clinical recommendation	NA (Review Article)	Pregnant women	NA	NA	The present clinical recommendation based on GRADE methodology gives a strong recommendation against treatment with metronidazole and a weak recommendation against treatment with clindamycin to reduce the risk of spontaneous preterm delivery
Hauth et al., 1995	Reduced incidence of preterm delivery with metronidazole and erythromycin in women with Bacterial Vaginosis (BV)	2:1 double-blind randomization to treatment with metronidazole and erythromycin (433 women) or placebo (191 women).	Pregnant Women	624 (433 Women assigned to metronidazole and erythromycin and 191 assigned to placebo arm)	7 days (250 mg/dose)	Treatment with metronidazole and erythromycin reduced rates of premature delivery in women with bacterial vaginosis and an increased risk for preterm delivery.
Howe 2017	Single-dose compared to multi-dose metronidazole for the treatment of trichomoniasis in	A systematic literature search was performed using search terms including metronidazole AND trichomoniasis AND	Adult Women	There were 487 articles that were assessed for relevance and quality. Of these articles, 6 met the eligibility criteria and	Single 2 g dose of metronidazole vs 500 mg twice a	In this meta-analysis of two different dose of metronidazole (MTZ) for treatment of trichomoniasis, treatment failure was 1.87 times (95% C.I. 1.23 -

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
	women: A meta-analysis	women. Embase, MEDLINE, and Clinicaltrials.gov were used to search for relevant studies as well as hand searching relevant articles.		were included in the final results	day for 7 days	2.82) more likely for 2 g single-dose versus multi-dose
Kong et al., 2013	Treatment of acne vulgaris during pregnancy and lactation	NA (Review Article)	Pregnant and lactating women	NA	NA	Topical medications are recommended as first-line treatment for acne vulgaris in pregnant and lactating women. These include antibiotics (erythromycin, clindamycin, metronidazole and dapsone), benzoyl peroxide, azelaic acid and salicylic acid. Oral agents and/or light-based therapy may be considered as second-line treatment
McDonald et al., 2007	Antibiotics for treating bacterial vaginosis in pregnancy	(Review Article) Randomized trials comparing antibiotic treatment with placebo or no treatment, or comparing two or more antibiotic	Pregnant Women	5888	NA	Antibiotic treatment can eradicate bacterial vaginosis (BV) in pregnancy. This review provides little evidence that screening and treating all pregnant women with asymptomatic bacterial vaginosis will prevent pre-

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
		regimens in pregnant women with bacterial vaginosis or intermediate vaginal flora				term births (PTB) and its consequences. However, there is some suggestion that treatment before 20 weeks' gestation may reduce the risk of PTB.
Meites et al., 2015	A Review of Evidence-Based Care of Symptomatic Trichomoniasis and Asymptomatic Trichomonas vaginalis Infections	NA (Review Article on Symptomatic Trichmoniasis and Asymptomatic Trichomonas vaginalis infections)	Pregnant women	Retrospective cohort study of 2829 pregnant women delivering at a major teaching hospital in Syracuse, New York.	NA	No association between metronidazole use during any trimester of pregnancy with any adverse outcomes.
Mitchell et al., 2009	Comparison of oral and vaginal metronidazole for treatment of bacterial vaginosis in pregnancy: impact on fastidious bacteria	NA (Review Article)	Pregnant Women	53 (30 women received oral metronidazole and 23 received intravaginal metronidazole)	Unknown	Both oral and vaginal metronidazole therapy in pregnant women result in a significant decrease in concentrations of most BV-associated anaerobic bacteria, with the exception that *Leptotrichia, Sneathia* and BVAB1 do not significantly decrease with vaginal metronidazole therapy. These data suggest that the route of antibiotic administration has

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
						a minor impact on bacterial eradication in pregnant women with BV
Muzny et al., 2020	Asymptomatic Bacterial Vaginosis: To Treat or Not to Treat?	NA (Review Article)	Pregnant women	Unknown	NA	Treatment of asymptomatic BV remains controversial. Additional studies are needed to further investigate the pathogenesis of BV, which will directly influence advances in its diagnosis, treatment, and prevention
Mylonas 2011	Antibiotic chemotherapy during pregnancy and lactation period: aspects for consideration	NA (Review Article)	Pregnant and lactating women	NA	NA	The use of metronidazole during pregnancy is permitted only if the indications for use have been strictly verified. Trichomonas infection should be treated with a single oral dose of 2 g. Parenteral administration is advisable only for dangerous anaerobic infections. Protracted vaginal application should be avoided, as it is not considered sufficiently effective and may also lead to prolonged exposure of the

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
						foetus. Metronidazole should be used over nimorazole and tinidazole. Termination of pregnancy or further diagnostics is not indicated.
Nielsen et al., 2014	IBD medications during pregnancy and lactation	NA (Review Article)	Pregnant and Lactating women	NA	NA	Metronidazole is excreted in breast milk. The American Academy of Pediatrics recommends that women receiving a single dose (2 g) of metronidazole should wait 12–24 h before breastfeeding, and an extended duration of metronidazole treatment during breastfeeding is associated with potential toxicity. Therefore, metronidazole is generally not recommended during breastfeeding
Palmsten, et al., 2015	The Most Commonly Dispensed Prescription Medications Among Pregnant Women Enrolled in the United	A cohort study of 1,106,757 pregnant women with live births using 2000-2007 Medicaid Analytic eXtract data. Outpatient pharmacy	Pregnant Women	NA	NA	During pregnancy, 82.5% of the cohort had a dispensing for one or more prescription medication. The most commonly dispensed medications during pregnancy included nitrofurantoin (21.6%), metronidazole (19.4%),

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
	States Medicaid Program	records were used to identify medication dispensings and reported the proportion of pregnancies that were dispensed at least one prescription medication. Maternal age and race and ethnicity–stratified estimates were compared using prevalence ratios (PR) and 95% confidence intervals (CI).				amoxicillin (18.0%), azithromycin (16.9%), and promethazine (13.5%). Proportions were highest among younger women for several medications; eg, nitrofurantoin (23.9% vs 15.4%; PR: 1.55, CI: 1.52-1.58), metronidazole (20.7% vs 12.0%; PR: 1.73, CI: 1.69-1.77), and azithromycin (21.1% vs 11.0%; PR: 1.93, CI: 1.89-1.97) were more common among women younger than 20 than among women aged 35 years or older.
Williams et al., 2021	Different classes of antibiotics given to women routinely for preventing infection at caesarean section (Review)	NA (Review Article) Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (2 December 2019) were searched, and reference lists of retrieved studies	Pregnant women	NA		At caesarean sections, antistaphylococcal cephalosporins and penicillins plus betalactamase inhibitors may be similarly effective at_preventing infections for the mother, although we did not find clear evidence for many important outcomes. In particular, we found no evidence describing the effects of these antibiotics on babies, nor any longer-term

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
						effects on women and children. This is particularly concerning for the studies giving the antibiotics prior to the surgical incision, as these antibiotics may reach the baby. For the other comparisons included in this review, data were sparse. Many studies were old and lacked information on study design and important outcomes, often including small numbers of women and few events. Research on drug-resistant antibiotics needs to be considered as well.
Valent et al., 2017	Effect of Post–Cesarean Delivery Oral Cephalexin and Metronidazole on Surgical Site Infection (SSI) Among Obese Women a	Single-center, double-blind, randomized clinical trial conducted to determine the efficacy of postoperative, prophylactic oral cephalexin plus	Women with a pre-pregnancy BMI of 30 or higher	404 (n=202 cephalexin-metronidazole; n= 201 placebo)	48 hours post operation/c esarian. (500 mg/dose)	Among obese women undergoing cesarean delivery who received standard preoperative cephalosporin prophylaxis, a postoperative 48-hour course of cephalexin-metronidazole, compared with placebo, reduced the rate of SSI

Author Year	Study/ Publication Title	Study Design	Study Population	Number of Patients Exposed/ Unexposed to Comparator	Timing of Exposure (drug/dose)	Outcome
	Randomized Clinical Trial	metronidazole compared with placebo for 48 hours after cesarean delivery for the prevention of SSI among obese women who receive standard preoperative cefazolin prophylaxis				within 30 days of delivery. For prevention of SSI among obese women after cesarean delivery, prophylactic oral cephalexin and metronidazole may be warranted There were no serious adverse events or allergic reactions reported for cephalexin or metronidazole

Source: Applicant's Submission dated 2/1/23, pages 15-30

Attachment B
Table 2: Exposure to Metronidazole (M) and the Risk of Preterm Birth (PTB)

Author	Source Population, Country	Study Design	Data Source	Exposure Definition	Main Outcome Definition	Results	Odds Ratio or Relative Risk (95% CI)
1. Morales[24] *et al*. 1994	N=80 United States	Randomised controlled trial (double blinded, placebo controlled)	Orlando Regional Medical Center	250 mg of metronidazole three times a day for 7 days	Preterm birth in women with a previous history	Exposed: 44 Unexposed: 36 Cases among exposed: 8 (18%) Cases among unexposed: 16 (44.4%)	OR: 0.27 (0.10-0.76)*
2. McDonald[28] *et al*. 1997	N=879 Australia	Randomised controlled trial (double blinded, placebo controlled)	Women's and Children's Hospital, North Adelaide	Exposure to oral metronidazole (400 mg) twice daily for two days	Spontaneous preterm birth less than 37 weeks of gestation	Exposed: 429 Unexposed: 428 Cases among exposed: 31 (7.2%) Cases among unexposed: 32 (7.5%)	OR: 0.14 (0.01-0.84)
3. Sorensen[21] *et al*. 1999	N=13451 Denmark	Retrospective cohort	Danish Medical Birth Registry	Exposure 30 days before conception, during the first trimester and any time during pregnancy	Delivery before 37 weeks of gestation	Exposed: 124 Unexposed: 13327 Cases among exposed: 6 (5%) Cases among unexposed: 93 (6%)	OR: 0.80 (0.35-1.83)
4. Carey[32] *et al*. 2000	N=1953 United States	Randomised controlled trial (placebo controlled)	National Institute of Child Health and Human Development	Two-dose regimen of 2000mg each in women with bacterial vaginosis and without trichomoniasis	Delivery before 37 weeks of gestation	Exposed: 966 Unexposed: 987 Cases among exposed: 116 (12%) Cases among unexposed: 121 (12.2%)	RR: 1.0 (0.8-1.2)
5. Goldenberg[10] *et al*. 2001	N=89 United States	Randomised controlled trial (placebo controlled)	National Institute of Child Health and Human Development	Two-dose regimen of 2000mg each in women with bacterial vaginosis and a positive test result for cervico-vaginal fetal fibronectin	Delivery before 37 weeks of gestation	Exposed: 48 Unexposed: 41 Cases among exposed: 4 (8.3%) Cases among unexposed: 6 (14.6%)	OR: 0.5 (0.13-1.92)*

[10]Goldenberg RL et al. Metronidazole treatment of women with a positive fetal fibronectin test result. Am J Obstet Gynaecol 2001; 185(2): 485-6.

6. Klebanoff[80] *et al*. 2001	N=617 United States	Randomised controlled trial (placebo controlled)	National Institute of Child Health and Human Development	Two-dose regimen of 2000mg each in women with asymptomatic trichomoniasis	Delivery before 37 weeks of gestation	Exposed: 320 Unexposed:297 Cases among exposed: 60 (19%) Cases among unexposed: 32 (10.7%)	RR: 1.8 (1.2-2.7)
7. Odendaal[11] *et al*. 2002	N=269 South Africa	Randomised controlled trial (placebo controlled)	Tygerberg Hospital	400 mg metronidazole, orally twice daily for 2 days	Delivery before 37 weeks	Exposed: 136 Unexposed: 133 Cases among exposed: 42 (30.8%) Cases among unexposed: 25 (18.8%)	OR: 1.93 (1.09-3.40)
8. Shennan[12] *et al*. 2006	N=100 United Kingdom	Randomised placebo-controlled trial	Fourteen UK hospitals	Metronidazole 400-mg for seven days	Delivery before 37 weeks of gestation	Exposed: 53 Unexposed: 47 Cases among exposed: 18 (39%) Cases among unexposed: 33 (62%)	RR: 1.6 (1.05 - 2.4)
9. Morency and Bujold[13], 2007	N=2779 Canada	Meta-Analysis	PubMed, Medline, and Embase Databases	Exposure to oral metronidazole	Delivery prior to 37 weeks' gestation	Exposed: 2779 Unexposed: 2531 Cases among exposed: 464 (16.7%) Cases among unexposed: 359 (14.2%)	OR: 1.10 (0.95-1.29)
10. Mann[14] *et al*. 2009	N=3579 United States	Retrospective cohort	Medicaid billing data and birth certificate records in South Carolina	Prescription for oral metronidazole	Delivery prior to 37 weeks' gestation	Exposed: 1436 Unexposed: 2143 Cases among exposed: 182 (12.7%) Cases among unexposed: 327 (15.3%)	HR: 0.69 (0.52-0.92)

*Crude or calculated using available data.

Source: Sheehy[5]

[11]Odendaal HJ et al. Preterm labour--is bacterial vaginosis involved? South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2002; 92(3): 231-4.

[12] Shennan A et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervico-vaginal fetal fibronectin: the PREMET Study. BJOG: Int J Obstet Gynecol 2006; 113(1): 65-74.

[13] Morency AM, Bujold E. The effect of second-trimester antibiotic therapy on the rate of preterm birth. J Obstet Gynaecol Canada: JOGC 2007; 29(1): 35-44.

[14]Mann JR et al. Treatment of trichomoniasis in pregnancy and preterm birth: an observational study. J Women's Health 2009; 18(4): 493-7.

Table 3: Exposure to Metronidazole in Association with Other Antibiotics and the Risk of PTB

Author	Source Population, Country	Study Design	Data Source	Exposure Definition	Main Outcome Definition	Results	Odds Ratio or Relative Risk (95% Confidence Intervals)
1. Norman[15] *et al*. 1994	N=81 South Africa	Randomised controlled trial.	Tygerberg Hospital (University of Stellenbosch), Somerset Hospital (University of Cape Town) and Coronation Hospital (University of Witwatersrand, Johannesburg)	Ampicillin 1 g intravenously repeated six hourly thereafter for 24 h, followed by amoxicillin 500 mg orally eight hourly for five days; concurrent metronidazole 1 g suppository, then 400 mg orally eight hourly for five days.	Delivery within seven days of admission.	Exposed: 43 Unexposed: 38 Cases among exposed: 16 (37.2%) Cases among unexposed: 23 (60.5%)	OR: 0.34 (0.13-0.94)
2. Hauth[27] *et al*. 1995	N=624 United States	Randomised controlled trial (double blinded, placebo controlled)	Public health clinics in Jefferson County, Alabama	Metronidazole (250 mg three times a day for 7 days) and erythromycin (333 mg three times a day for 14 days)	Rate of delivery before 37 weeks' gestation among women with and without bacterial vaginosis	Exposed:433 Unexposed: 191 Cases among exposed: 112 (26%) Cases among unexposed: 68 (36%)	RR: 1.1 (0.8-1.7) for all subjects RR: 1.6 (1.1-2.1) for subjects with bacterial vaginosis
3. Svare[29] *et al*. 1997	N=112 Denmark	Randomised controlled trial (double blinded, placebo controlled)	Six obstetric departments in the Copenhagen area	Eight days intravenous and oral treatment with ampicillin and metronidazole	Rate of delivery before 37 weeks' gestation among	Exposed: 59 Unexposed: 51 Cases among exposed: 25 (42%) Cases among unexposed: 33 (65%)	OR: 0.41 (0.19-0.87)

[15] Norman K et al. Ampicillin and metronidazole treatment in preterm labour: a multi-centre, randomised controlled trial. Br J Obstet Gynaecol. 1994; 101(5): 404-8.

4. Andrews[16] *et al*. 2003	N=703 United States	Randomised controlled trial	Department of Obstetrics and Gynecology, Center for Research in Women's Health	Metronidazole (250 mg orally three times per day) and erythromycin (250 mg orally four times per day)	Delivery before 37 weeks' gestation after preterm labor or premature membrane rupture	Exposed: 347 Unexposed: 356 Cases among exposed: 50 (14.4%) Cases among unexposed: 44 (12.4%)	OR: 1.17 (0.80-1.70)
5. Camargo[17] *et al*. 2005	N=205 Brazil	Retrospective cohort	Obstetric Service at the Universidade Estadual de Campinas	Metronidazole, 750 mg/day, orally for seven days; metronidazole, tinidazole or secnidazole, 2 g orally, single dose	Delivery before 37 weeks of gestation	Exposed: 134 Unexposed: 71 Cases among exposed: 5 (3.7%) Cases among unexposed: 16 (22.5)	OR: 0.13 (0.05-0.38)*
6. Okun[18] *et al.* 2005	N=6052 Canada	Systematic review	Pre-Med, Medline, Embase and the Cochrane Library	Exposure to metronidazole	Delivery before 37 weeks of gestation	Exposed: 3146 Unexposed: 2906 Cases among exposed: 426 (13.5%) Cases among unexposed: 83 (13.17%)	OR: 0.93 (0.70-1.22)
7. Sen[19] *et al.* 2005	N=224 India	Randomised controlled trial	Government hospital in Kolkata, India	Metronidazole 200 mg eight hourly for seven days and + cephalexin 500 mg capsules 12 hourly for five days.	Delivery before 37 weeks of gestation	Exposed: 112 Unexposed: 112 Cases among exposed: 9 (7.9%) Cases among unexposed: 12 (10.7%)	OR: 0.60 (0.19-1.88)*

*Crude or calculated using available data.

Source: Sheehy[5]

[16] Andrews WW et al. Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women. Obstet Gynecol 2003; 101(5 Pt 1): 847-55.

[17] Camargo RP et al. Impact of treatment for bacterial vaginosis on prematurity among Brazilian pregnant women: a retrospective cohort study. Sao Paulo Med J 2005; 123(3): 108-12.

[18] Okun N et al. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: Sys Rev Obstet Gynecol 2005; 105(4): 857-68.

[19] Sen A et al. Routine use of antimicrobials by pregnant Indian women does not improve birth outcome: a randomized controlled trial. J Health Popul Nutr 2005; 23(3): 236-44.

Table 4: Exposure to Metronidazole and the Risk of Birth Defects.

Author	Source Population, Country	Study Design	Data Source	Exposure Definition	Outcome Definition	Results	Chi squared, Odds Ratio or Relative Risk or Other (95% CI)
1. Scott-Gray[20], 1964	N=183 United Kingdom	Prospective cohort	Edinburgh Royal Hospital	Exposure during the first or third trimester of pregnancy with 200mg of metronidazole	Any birth defect	Exposed:79 Unexposed: 104 Cases among exposed: 0 (0%) Cases among unexposed: 4 (3.8%)	Chi squared: 1.57 p=0.21
2. Robinson and Mirchanda-ni[21], 1965	N=190 United States	Prospective cohort		Exposure during the first or third trimester of pregnancy	Any birth defect	Exposed:14 Unexposed: 196 Cases among exposed: 0 (0%) Cases among unexposed: 4 (2%)	Chi squared: 0.158 p=0.69
3. Rodin and Hass[22] 1966	N=32 United Kingdom	Prospective cohort	Whitechapel Clinic - London Hospital	Exposure during the first trimester of pregnancy, 200mg of metronidazole, T.I.D, 1 week	Any birth defect	Exposed:13 Unexposed: 19 Cases among exposed: 0 (0%) Cases among unexposed: 0	No cases of birth defects
4. Peterson[23] *et al*. 1966	N=128 United States	Prospective cohort		Exposure during the first or third trimester of pregnancy	Any birth defect	Exposed: 54 Unexposed: 74 Cases among exposed: 0 (0%) Cases among unexposed: 1 (1.35%)	Chi squared: 0.025 p=0.87
5. Heinonen[12] *et al*. 1977	N=50282 United States	Prospective cohort		Exposure during the first of pregnancy	Major birth defects	Exposed: 31 Unexposed: 50251 Cases among exposed: 4 (13%) Cases among unexposed: 3244 (6.4%)	RR: 2.15 (0.75-6.13)
6. Morgan[24], 1978	N=350 United States	Retrospec-tive cohort		Exposure during the first of pregnancy	Any birth defect	Exposed: 63 Unexposed: 287 Cases among exposed: 2 (3.2%) Cases among unexposed: 8 (2.8%)	RR: 1.14 (0.23-5.52)

[20] Scott-Gray M. Metronidazole in Obstetric Practice. J Obstet Gynaecol Br Commonwealth 1964; 71: 82-5.
[21] Robinson SC, Mirchandani G. Trichomonas vaginalis. V. Further observations on metronidazole (Flagyl) (including infant follow-up). Am J Obstet Gynecol 1965; 93(4): 502-5.
[22] Rodin P, Hass G. Metronidazole and pregnancy. Br J Vener Dis 1966; 42(3): 210-2.
[23] Peterson WF et al. Metronidazole in pregnancy. Am J Obstet Gynecol 1966; 94(3): 243-9.

[24] Morgan I. Metronidazole treatment in pregnancy. Int J Gynaecol Obstet: the official organ of the Int Federation Gynaecol Obstet 1978;15(6):501-2.

7. Rosa[15] *et al*. 1987	N=104339 United States	Retrospective cohort	Computerized Medicaid records	Exposure to miconazole, clotrimazole, nystatin, candicidin, aminacrine compounds, and metronidazole during the first trimester of pregnancy	Any birth defect	Exposed: 1083 Unexposed: 103256 Cases among exposed: 63 (5.8%) Cases among unexposed: 6501 (6.3%)	RR: 0.92 (0.8-1.6)
8. Piper[16] *et al*. 1993	N=2774 United States	Retrospective cohort	Tennessee Medicaid files	Exposure during the first trimester of pregnancy	Major birth defects	Exposed: 1387 Unexposed: 1387 Cases among exposed: 96 (7%) Cases among unexposed: 80 (5.7%)	RR: 1.2 (0.9-1.6)
9. Burtin[17] *et al*. 1993	N=104872 Canada	Meta-Analysis		Exposure during the first or third trimester of pregnancy	Any birth defect		OR: 0.93 (0.73-1.18)
10. Caro-Paton[18] *et al*. 1997	N=199451 Spain	Meta-Analysis		Exposure during the first trimester of pregnancy	Any birth defect		OR=1.08 (0.90-1.29)
11. Czeizel and Rockenbauer[19], 1998	N=47963 Hungary	Case-control	Hungarian Surveillance of Congenital Abnormalities database	Exposure during the first trimester of pregnancy, 250mg of metronidazole	Major birth defects	Cases: 17300 Controls: 30663 Exposed cases: 665 (3.8%) Exposed controls: 1041 (3.4%)	OR: 1.14 (0.89-1.46)
12. Sorensen[21] *et al*. 1999	N=13451 Denmark	Retrospective cohort	Danish Medical Birth Registry	Exposure 30 days before conception and during the first trimester of pregnancy	Any birth defect	Exposed: 124 Unexposed: 13327 Cases among exposed: 3 (2.4%) Cases among unexposed: 693 (5.2%)	OR: 0.44 (0.11-1.81)
13. Diav-Citrin[22] *et al*., 2001	N= 791 Israel	Retrospective cohort	Chart reviews and electronic data from New York State hospital	Exposure during the first trimester of pregnancy	Major birth defects	Exposed: 205 Unexposed: 586 Cases among exposed: 3 (1.45%) Cases among unexposed: 8 (1.3%)	RR:1.13 (0.30-4.23)

Source: Sheehy[5]

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/

JANE E LIEDTKA
07/21/2023 07:53:39 AM

JANE E LIEDTKA on behalf of TAMARA N JOHNSON
07/21/2023 07:54:51 AM

LYNNE P YAO
07/21/2023 08:04:07 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	July 5, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216755
Product Name, Dosage Form, and Strength:	Likmez (metronidazole) Oral Suspension, 500 mg/5 mL
Applicant/Sponsor Name:	Saptalis Pharmaceuticals, LLC (Saptalis)
TTT ID #:	2022-2881-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on June 29, 2023 for Likmez. The Division of Anti-Infectives (DAI) requested that we review the revised container label for Likmez (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

As part of their June 29, 2023 submission,[b] Saptalis provides clarification that they intend to use only a numeric format for expressing their expiration date (i.e., the month format expressed as 'MM' will use numbers). We find the aforementioned clarification that only a numeric format for expressing the expiration date acceptable from a medication error perspective.

[a] Myers, D. Label and Labeling Review for Likmez (NDA 216755). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 06. TTT ID No.: 2022-2881.

[b] Saptalis Pharmaceuticals, LLC. Cover Letter: Response to Information Request – DMEPA Recommendations for Likmez (NDA 216755). Hauppauge (NY): Saptalis; 2023 JUN 29. Available from: \\CDSESUB1\EVSPROD\nda216755\0019\m1\us\cover-letter-216755-0019.pdf.

3 CONCLUSION

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

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

---

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/

DEBORAH E MYERS
07/05/2023 09:50:23 AM

VALERIE S VAUGHAN
07/05/2023 10:06:48 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	June 6, 2023
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 216755
Product Name, Dosage Form, and Strength:	Likmez (metronidazole) Oral Suspension, 500 mg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Saptalis Pharmaceuticals, LLC (Saptalis)
FDA Received Date:	November 23, 2022
TTT ID #:	2022-2881
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Likmez (metronidazole) Oral Suspension, the Division of Anti-Infectives (DAI) requested that we review the proposed Likmez prescribing information (PI) and container label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND / REGULATORY HISTORY

NDA 216755 is a 505(b)(2) NDA and the listed drug product is Flagyl, NDA 012623.

2 MATERIALS 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Label and Labeling	F

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 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI) and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Saptalis Pharmaceuticals, LLC.

4 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented, under the heading "*Dosage and Administration*" subheading "*Trichomoniasis*", the included text "One-day treatment – 2 g (20 mL) of…" includes the abbreviation "g" which is not defined.	Abbreviations can be a source of misinterpreted and result in confusion if not appropriately defined.	To minimize the potential for misinterpretation, replace the occurrence of the abbreviation "g" with the word "grams." For example, "One-day treatment – 2 grams (20 mL) of…"
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented in Section 2.1 *Trichomoniasis,* the route of administration (i.e., orally) is not included, which is inconsistent with the text in Sections 2.2 *Amebiasis* and 2.3 *Anaerobic Bacterial Infections* which include the route of administration.	To minimize the risk of wrong route of administration errors, the route of administration should be included consistently throughout the *Dosage and Administration* Section.	To help avoid medication errors involving wrong route of administration and provide consistency throughout the *Dosage and Administration* Section, we recommend adding the route of administration (i.e., orally) in Section 2.1 *Trichomoniasis*. For example, "*One-day treatment* – 2 g (20 mL) of LIKMEZ, given orally…" and "*Seven-day course of treatment* – 250 mg (2.5 mL) orally…"
2.	As currently presented in Section 2.1 *Trichomoniasis*, the included text "One-day treatment – 2 g (20 mL) of…divided doses of 1 g (10 mL)…" includes the abbreviation "g" which is not defined.	Abbreviations can be a source of misinterpreted and result in confusion if not appropriately defined.	To minimize the potential for misinterpretation, replace the occurrences of the abbreviation "g" with the word "gram(s)." For example, "One-day treatment – 2 grams (20 mL) of… divided doses of 1 gram (10 mL)…"

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	As currently presented, no statement is present to instruct patients, or their caregivers, to use a calibrated oral dosing device to measure the appropriate dose.	Dosing errors could occur with the use of household teaspoons or tablespoons.	Add to the current subsection 2.5 *Important Administration Instructions* the following statements: "Use a calibrated oral dosing device to correctly measure the prescribed dose of medication. Do not use household teaspoons or tablespoons to measure doses. Calibrated oral dosing devices may be obtained from the pharmacy."
Full Prescribing Information – Section 3 *Dosage Forms and Strengths*			
1.	A description of the dosage form is not provided (e.g., color).	A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(4)(ii).	Provide a description of identifying characteristics of the Oral Suspension in accordance with 21 CFR 201.57(c)(4)(ii).
Full Prescribing Information – Section 17 *Patient Counseling*			
1.	As currently presented, no statement is present to instruct patients, or their caregivers, to use a calibrated oral dosing device to measure the appropriate dose.	Dosing errors could occur with the use of household teaspoons or tablespoons.	Under the subheading Administration Instructions, following the current bullet point "Ensure the prescribed dose of LIKMEZ oral suspension is taken as directed," we recommend adding the following statements: • Use a calibrated oral dosing device to correctly measure the prescribed dose of medication. Do not use a household teaspoon or tablespoon to measure doses. Calibrated oral dosing devices may be

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			obtained from the pharmacy.

5 RECOMMENDATIONS FOR SAPTALIS PHARMACEUTICALS, LLC

Table 3. Identified Issues and Recommendations for Saptalis Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the format for expiration date is defined as "MM/YYYY." However, it is unclear how the month will be expressed.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. For example, presenting the month as 'MA' or 'JU' does not clearly communicate whether 'MA' or 'JU' is for the months of March or May and June or July, respectively.	Clarify how you intend to express the month within the expiration date statement. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.

Table 3. Identified Issues and Recommendations for Saptalis Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	As currently presented, it is noted that the "Unvarnished Area" is intended to include either "batch details" (i.e., "LOT: XXXXXXX EXP: (b) (4)") *OR* the product identifier information (i.e. 2-D Matrix, GTIN, LOT, Expiration date, and serial number.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. For additional details, See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).[a]	We recommend that you add a place holder to the container label for the product identifier.
3.	As currently presented, the terminology within the statement of dosage (i.e., "(b) (4)") is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage to read, "Dosage: see Prescribing Information."

[a] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Likmez that Saptalis Pharmaceuticals, LLC submitted on November 23, 2022, and the reference product (RP).[b]

Table 4. Relevant Product Information for Reference Product and Likmez		
Product Name	Flagyl	Likmez
Application Type and Number	NDA 012623	NDA 216755
Initial Approval Date	July 18, 1963	N/A
Active Ingredient	metronidazole	
Indication	• Symptomatic Trichomoniasis • Asymptomatic Trichomoniasis • Treatment of Asymptomatic Sexual Partners • Amebiasis • Anaerobic Bacterial Infections	For the treatment of: Trichomoniasis • Symptomatic trichomoniasis • Asymptomatic trichomoniasis • Asymptomatic sexual partners Amebiasis Anaerobic bacterial infections
Route of Administration	oral	
Dosage Form	tablets	Oral Suspension
Strength	250 mg 500 mg	500 mg/5 mL (100 mg/mL)
Dose and Frequency	Trichomoniasis: *One-day treatment* – two grams of FLAGYL, given either as a single dose or in two divided doses of one gram each, given in the same day. *Seven-day course of treatment* – 250 mg three	Trichomoniasis: *One-day treatment*: 2 g (20 mL) given as a single dose or in two divided doses of 1 g (10 mL) each, given in the same day. *Seven-day course of treatment*: 250 mg (2.5 mL) 3 times daily for 7 consecutive days.

[b] Flagyl [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. DEC 2021 [Cited 2023 APR 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/012623s069lbl.pdf.

	times daily for seven consecutive days. Amebiasis: *Adults*: For acute intestinal amebiasis (acute amebic dysentery): 750 mg orally three times daily for 5 to 10 days. For amebic liver abscess: 500 mg or 750 mg orally three times daily for 5 to 10 days. *Pediatric patients*: 35 to 50 mg/kg/24 hours, divided into three doses, orally for 10 days. Anaerobic Bacterial Infections: In the treatment of most serious anaerobic infections, intravenous metronidazole is usually administered initially. *The usual adult oral dosage* is 7.5 mg/kg every six hours (approx. 500 mg for a 70-kg adult). A maximum of 4 g should not be exceeded during a 24-hour period. *The usual duration of therapy* is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.	Amebiasis: *Adults*: For acute intestinal amebiasis (acute amebic dysentery): 750 mg (7.5 mL) orally three times daily for 5 days to 10 days. For amebic liver abscess: 500 mg (5 mL) or 750 mg (7.5 mL) orally three times daily for 5 days to 10 days. *Pediatric patients*: 35 mg/kg/24 hours to 50 mg/kg/24 hours, divided into three doses, orally for 10 days. Anaerobic bacterial infections: In the treatment of most serious anaerobic infections, intravenous metronidazole is usually administered initially. *The usual adult oral dosage* is 7.5 mg/kg every six hours (approx. 500 mg (5 mL) for a 70-kg adult). A maximum of 4 g (40 mL) should not be exceeded during a 24-hour period. *The usual duration of therapy* is 7 days to 10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.
How Supplied	250 mg tablets: • Bottle of 50 • Bottle of 100 500 mg tablets: • Bottle of 50 Bottle of 100	In a 250 mL white High Density Polyethylene (HDPE) round bottle with child-resistant cap (CRC) containing 200 mL.
Storage	Store below 25°C (77°F) and protect from light.	Store between 20°C to 25°C (68°F to 77°F); (b) (4) to 15°C to 30°C (59°F to 86°F) [See USP

		Controlled Room Temperature]. *Do not freeze*.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 10, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "Likmez," "NDA 216755," and "metronidazole." Our search identified two previous reviews[c,d], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Winiarski, A. Label and Labeling Review for Pylera (NDA 050786/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JAN 09. OSE RCM No.: 2012-2258.

[d] Winiarski, A. Label and Labeling Review for Pylera (NDA 050786/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 AUG 14. OSE RCM No.: 2012-1053.

APPENDIX F. LABELS AND LABELING

F.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Likmez labels and labeling submitted by Saptalis Pharmaceuticals, LLC.

- Container label received on November 23, 2022
- Prescribing Information (Image not shown) received on November 23, 2022, available from: \\CDSESUB1\EVSPROD\nda216755\0001\m1\us\draft-labeling-text-word.docx.

F.2 Label and Labeling Images

Container label

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

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/

DEBORAH E MYERS
06/06/2023 12:01:31 PM

VALERIE S VAUGHAN
06/06/2023 12:09:42 PM