CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215500Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: November 15, 2023

To: Ashley Lane, MS, Consumer Safety Officer, DO2

Elizabeth Duke, Associate Director for Labeling

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for IWILFIN (eflornithine) tablets, for oral use

NDA: 215500

In response to DO2's consult request dated December 13, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for IWILFIN™ (eflornithine) tablets, for oral use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DO2 on November 1, 2023, and updated on November 7, 2023, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed and comments on the proposed PPI were sent under separate cover on November 8, 2023.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 7, 2023, and our comments are provided below.

OPDP notes the applicant's recommendation (b) (4). We are concerned that the use of (b) (4)" is too restrictive and may be confusing to the Healthcare provider or patient. We note the review division's proposal to change (b) (4)" to "soft food or liquid" and agree with this recommendation. We propose that the Carton and Container labeling be updated to reflect these changes.

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

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Reference ID: 5277723

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/s/

MISPA L AJUA-ALEMANJI
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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:	November 8, 2023
To:	Ashley Lane, MS Consumer Safety Officer **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Mispa Ajua-Alemanji, PharmD Regulatory Review Office **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	IWILFIN (eflornithine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215500
Applicant:	USWM, LLC

1 INTRODUCTION

On November 21, 2022, USWM, LLC submitted for the Agency's review an original New Drug Application (NDA) 215500 for IWILFIN (eflornithine) tablets. The proposed indication for IWILFIN (eflornithine) tablets is to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have completed multiagent, multimodality therapy.

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 Oncology II (DO2) on December 13, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IWILFIN (eflornithine) tablets.

2 MATERIAL REVIEWED

- Draft IWILFIN (eflornithine) tablets PPI received on November 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 1, 2023.
- Draft IWILFIN (eflornithine) tablets Prescribing Information (PI) received on November 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 1, 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. In our review of the PPI the target reading level is at or below an 8th grade 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 reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- 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.

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/s/

RUTH I MAYROSH
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MISPA L AJUA-ALEMANJI
11/08/2023 01:44:42 PM

LASHAWN M GRIFFITHS
11/08/2023 02:11:18 PM

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

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

Memorandum

Date: July 3, 2023

To: Ashley Lane, MS, Consumer Safety Officer, DO2

Elizabeth Duke, Associate Director for Labeling

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for IWILFIN (eflornithine) tablets, for oral use

NDA: 215500

This memo is in response to DO2' s labeling consult request dated December 13, 2022. OPDP defers comment on the proposed labeling at this time, and requests that DO2 submit a new consult request during the subsequent review cycle.

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

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/s/

MISPA L AJUA-ALEMANJI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	May 4, 2023
To:	Ashley Lane, MS Consumer Safety Officer **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI)
Drug Name (established name):	IWILFIN (eflornithine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215500
Applicant:	USWM, LLC

Reference ID: 5169088

1 INTRODUCTION

On November 21, 2022, USWM, LLC submitted for the Agency's review an original New Drug Application (NDA) 215500 for IWILFIN (eflornithine) tablets. The proposed indication for IWILFIN (eflornithine) tablets is to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have completed multiagent, multimodality therapy.

On December 13, 2022, the Division of Oncology II (DO2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for IWILFIN (eflornithine) tablets.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for IWILFIN (eflornithine) tablets.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DO2 plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

RUTH I MAYROSH
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LASHAWN M GRIFFITHS
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Clinical Inspection Summary

Date	April 19, 2023
From	Lee Pai-Scherf, MD Michele Fedowitz, acting Team Lead Jenn Sellers, MD, Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE/OSI
To	Elizabeth Duke, MD, Medical Officer Diana Bradford, MD, Team Lead Division of Oncology 2/OOP
NDA/BLA #	NDA 215500
Applicant	US WorldMeds, LLC
Drug	Eflornithine Hydrochloride (DFMO)
NME (Yes/No)	No
Therapeutic Classification	Ornithine decarboxylase (ODC) inhibitor
Proposed Indication(s)	To reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have completed multiagent, multimodality therapy
Consultation Request Date	December 19, 2022, amended January 20, 2023
Summary Goal Date	April 21, 2023
Action Goal Date	May 20, 2023
PDUFA Date	May 21, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study NMTRC003b and Study BCC001, a retrospective chart review, were submitted to the Agency in support of a 505(b)(2) NDA 215500 for eflornithine hydrochloride (DFMO) for the above proposed indication. The application relies on external data from Study ANBL0032, conducted by Children's Oncology Group (COG), to provide an external control cohort for the single-arm Studies NMTRC003b and BCC001.

Two clinical investigators (CI), Drs. Deanna Mitchell (site # 08), Keith August (site # 11), the sponsor-investigator, Dr. Giselle Sholler, the NDA sponsor, US WorldMeds, LLC, and the imaging CRO, (b) (4) were inspected. In addition, an Op-13 investigation was conducted for COG to ensure the reliability and acceptance of the transferred data to be used as an external control for Study NMTRC003b.

The above inspections did not reveal significant findings. Studies NMTRC003b and BCC001 appear to have been conducted adequately and the data generated by the inspected clinical investigators, the imaging CRO and submitted by the sponsor appear acceptable in support of the proposed indication.

The investigation of COG revealed no discrepancies between the data submitted to the NDA and the study data from ANBL0032 housed at COG that served as the external control for Study NMTRC003b.

Of note, the inspection results of Dr. Mitchell are based on a summary provided by the FDA field investigator and are therefore preliminary. If significantly new or different information is contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

II. BACKGROUND

DFMO intravenously injectable formulation was approved in 1990 (Ornidyl, NDA019879) for the treatment of Trypanosoma brucei gambiense infection (sleeping sickness) and in 2018, as a topical cream formulation for the treatment of unwanted facial hair in women (Vaniqa, NDA 021145). DFMO is not currently approved for high-risk neuroblastoma (HRNB) in any market.

This 505(b)(2) NDA relies on literature reports, FDA's previous findings of safety, pharmacology/toxicology data submitted to NDA 019879 and efficacy data from a phase II, single-arm study of DFMO (NMTRC003b) and retrospective chart review study BCC001 in patients with HRNB who had achieved remission following multimodality therapy.

Study NMTRC003 began in 2012 under the research IND 144875 sponsored by the sponsor-investigator Dr. Giselle Sholler. In December 2017, the source of the study drug was changed and due to this change, the study was amended (amendment 5/Study NMRTC003b) to use the new source of DFMO. In September 2020, IND 144875 was transferred to commercial sponsor US WorldMeds to further develop DFMO for HRNB. Due to the change in DFMO supplier, the data in the NMTRC003 database (using prior DFMO) were not available to the commercial sponsor for registration purposes. However, US WorldMeds was able to obtain data for patients on prior DFMO by access to a retrospective chart review of the BCC database ("BCC001").

Study BCC001 was a retrospective chart review study, designed to collect data on any HRNB patient treated with DFMO at a Beat Childhood Cancer Research Consortium (BCC) site. All patients who had completed the NMTRC003 study taking prior DFMO were contained in the BCC001 study database and were included in the efficacy analyses for this NDA.

The application relies on external control data from Study ANBL0032 to evaluate event-free survival and overall survival data from Study NMTRC003b. Study ANBL0032 was conducted by the Children's Oncology Group (COG). Data from ANBL0032 was previously submitted to the FDA by United Therapeutics Corporation under BLA 125516 in 2014 to support an indication for ch14.18 (dinutixumab) for the treatment of patients with high-risk neuroblastoma. Approval of dinutixumab was granted in March 2015.

Two clinical investigators were identified for inspection by DO2 and OSI: Drs. Deanna Mitchell (Site # 08), and Keith August (Site # 11), taking into consideration the total number of subjects enrolled and safety and efficacy parameters. The sponsor-investigator, Dr. Giselle Sholler at BCC and the commercial sponsor, US WorldMeds, were selected for inspection to examine the conduct and oversight of Studies NMTRC003b and BCC001. (b) (4) was selected for inspection to evaluate the independent central review of imaging data and verify the primary efficacy endpoint of event-free-survival (EF) in a large number of subjects. Investigation of Children's Oncology Group was requested to verify reliability of the external control data used for statistical comparison for the efficacy endpoints.

III. RESULTS (by site):

1. **Dr. Keith August (site # 11)**
   2401 Gillham Road
   Kansas City, MO 64108

   Inspection dates: 01/30/2023 – 02/02/2023

   Dr. August was inspected as a surveillance inspection for NMTRC003b and BCC001. This was the first inspection for Dr. August.

   At the time of the inspection, the site had enrolled 7 subjects in study NMTRC003b, of which, 6 subjects had completed study treatment and 1 subject had relapsed. Five subjects were included in the retrospective chart review study (BCC001), of which, 2 subjects had died and 3 discontinued due to disease progression at the time of the data cut-off date.

   For study NBTRC003b, source records for all 7 subjects enrolled at the site were reviewed. Records reviewed include study eligibility, informed consent forms, medical history, protocol adherence, concomitant medication documentation, adverse event (AE) documentation, laboratory results and assessments. All subjects met protocol specified inclusion and exclusion criteria and had signed informed consent prior to study activities. There was no underreporting of AEs, serious AEs, or significant protocol deviations noted for subjects enrolled in study NMTRC003b. No discrepancies were observed between the data listings submitted to the NDA and source records.

   The primary efficacy assessment was verifiable, as radiographic scans were performed at protocol specified timepoints and submitted to the sponsor for central verification of event free survival (EFS) by the imaging CRO.

   For study BCC001, case report forms for all 5 subjects and the documentation of the retrospective chart reviews were assessed. Data reviewed included, but was not limited to subject demographics, medical histories, disease characteristics, previous cancer

treatment data, study drug exposure, laboratory results, and tumor assessment.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. August at the conclusion of the inspection.

2. Dr. Deanna Mitchell (site # 08)
S 100 Michigan Street NE
MC 085 Grand Rapids
MI 49503

Inspection dates: 02/13/2023 – 02/17/2023

The official establishment inspection report (EIR) is pending. The review below is from the summary close out email and communications with the inspector during the inspection. This report will be updated after review of the official EIR, if relevant additional information is included.

Dr. Mitchell was inspected as a surveillance inspection for Study NMTRC003b and retrospective chart review for Study BCC001. This was the first inspection for Dr. Mitchell.

The site enrolled 26 subjects in Study NBTRC003b and 12 subjects in Study BCC001. At the time of the inspection, no subjects were on active study treatment, or had previously discontinued treatment.

For Study NBTRC003b, source documents for 9 subjects were reviewed during the inspection. For Study NBTRC003b, individual patient source binders, procedures, adverse event records, follow up communications with external providers. All reviewed subjects met protocol specified inclusion and exclusion criteria and signed informed consent prior to study activities. There was no underreporting of AEs or significant protocol deviations for subjects enrolled in NBTRC003b. Additional records reviewed include IRB documents, financial disclosure forms, pharmacy records, case report forms, monitoring and training records of study.

For Study BCC001, records for all 12 subjects included in the retrospective chart review were reviewed. Records from various sources were reviewed and include electronic medical records from various providers (PCPs), transfer summaries, dosing logs, and 5-year follow up records, including death certificates, when available. Records reviewed were consistent with the data submitted to the NDA.

For all NBTRC003b subjects reviewed, radiographic scans were performed at protocol specified timepoints and submitted to the Sponsor for central verification of primary efficacy endpoint of EFS by the imaging CRO.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Mitchell at the conclusion of the inspection.

The above information was based on preliminary communication with the field inspector. A Clinical Inspection Summary addendum will be generated if conclusions change based upon receipt and review of the official EIR for the site.

3. **Giselle Sholler, MD (sponsor-investigator)**
Beat Childhood Cancer (BCC)
Levine Children's Hospital
1025 Morehead Medical Drive, Suite 600
Charlotte, NC 28203

Inspection dates: 01/30/2023 – 02/06/2023

The on-site inspection assessed Dr. Sholler's oversight responsibilities for Study NMTRC003b and Study BCC001. This was the first sponsor inspection of Dr. Sholler.

The inspection included, but was not limited to, review of the following documents: selection of clinical investigators and study monitors, training records, monitoring plans and visit reports, data collection and handling procedures, safety/adverse event reporting and protocol deviations, selected clinical site files. Other documents reviewed include investigational product accountability records, Form FDA 1572, financial disclosure, contract agreements, standard operating procedures (SOPs), and the Trial Master Files.

Records related to four CIs: two were selected for inspection (Deanna Mitchell, site # 08, Dr. Keith August, site # 11) and two additional CIs (Virginia Harrod, site # 18, and Jonathon Metts, site # 24) were randomly selected for a targeted record review which included, but not limited to, site personnel qualification and training material, monitoring logs, adverse event reporting, IRB approval and associated documents, and site investigational accountability records. The inspection found that Dr. Sholler provided adequate oversight, monitoring and performed her responsibilities according to the regulatory requirements.

The inspection did not reveal any significant inspectional observations and found no regulatory violations. No Form FDA 483 was issued to Dr. Sholler at the conclusion of the inspection.

4. **US WorldMeds, LLC** (Sponsor)
4441 Springdale Road
Louisville, KY 40241

Inspection dates: 02/02/2023 – 02/09/2023

The inspection assessed US WorldMeds' oversight responsibilities for NMTRC 003B, BCC001 and external cohort data obtained from the Children's Oncology Group. US WorldMeds was previously inspected on 01/19/2018 thru 02/23/2018 and was classified as No Action Indicated (NAI).

US WorldMeds assumed sponsorship of IND 114875 from Dr. Giselle Sholler in September 2020. Data from Studies NMRTC003b and BCC001 were provided to USWM by Dr. Sholler for analysis and submission. The oversight and monitoring responsibilities remained with Dr. Sholler. In addition, BCC/USWM received real world data from the COG from Study ANBL0032 to use as external control in the final analysis. USWM was responsible the overall data management, programming and statistical analysis for the NMRTC 003B clinical study reports and submission to the FDA.

The inspection covered the review of organizational charts, written agreements, standard operating procedures, training records, operation qualification performed on the SAS software, statistical analysis plan and data verification for Studies NMTRC003b, BCC001 and ANBL0032.

The inspection verified that data receipt from various sources (BCC, COG, Imaging CRO) for efficacy and safety analysis were conducted according to specified agreements and charters. In addition, the inspection verified that the electronic platforms used for receipt, storage and transfer of data complied with applicable regulations and were password protected.

The accuracy of the data submitted to the NDA was verified by cross checking with USWM's data base for 30 randomly selected subjects enrolled in Study NMTR003b (5 subjects from Site # 07 and 5 subjects from Site # 03), BCC001 (5 subjects enrolled in site # 08) and in 15 out of 40 subjects identified by the review division as subjects of interest, in Study ANBL0332. No discrepancies were noted between the data submitted to the NDA and the USWM's database.

The inspection found no regulatory violations and the USWM data and records appeared adequate. No Form FDA 483 was issued to US WorldMeds at the conclusion of the inspection.

5. (b) (4) (Central Imaging Services CRO)
(b) (4)

Inspection dates: 01/25/2023 – 01/27/2023

(b) (4) was inspected as data audit and surveillance inspection for Study NMTRC003b. This was the first inspection of (b) (4) by the FDA.

The inspection covered the evaluation of data reliability and study conduct for the imaging CRO (b) (4). Documents reviewed included the review of the following records: contract agreement with US WorldMeds and vendors for various activities, written procedures/ charters, training records by vendors, record retention, and the process of receiving scans or images from the Sponsor, evaluation by independent readers and data transfer activities to the sponsor.

For Study NMTRC003b, the radiographic images were retrospectively collected by the Sponsor and provided to (b) (4) who confirmed that the unscheduled visits were incorporated within the timepoints for each subject. Scans and results were stored in the vendor DSG's eCASELink 8.0 database. (b) (4) provides weekly reported to the sponsor in the form of a data transfer file. The inspection found no procedure deviations from the pre-specified procedures and charters.

Records from 25 subjects identified by the review division as the cohort of interest, were verified for accuracy by comparing the data submitted to the NDA against the data points at (b) (4). Review included date of assessment, radiology 1 and 2 reads and adjudication, if warranted, and the final assessment. No discrepancies were noted between the datapoints submitted to the NDA and the database provided by (b) (4).

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to (b) (4) at the conclusion of the inspection.

6. Children Oncology Group (COG)
COG Statistics and Data Center
1333 S. Mayflower Ave, Suite 260
Monrovia, CA 91016

Investigation dates: 03/07/2023 – 03/09/2023

Under a data transfer agreement, COG provided BCC/US WorldMeds with a limited dataset from Study ANBL0032 to serve as external matching control for the single arm Study NMTRC003b.

The purpose of this investigation was to verify COG's data management processes and procedures, specifically ANBL0032 study data storage, curation, aggregation, and transfer procedures from COG to BCC/US WorldMeds. The investigation verified that the electronic platforms used by COG to store and transfer the data to BCC/US WorldMeds complied with applicable regulations and were password protected and that data transfer agreements between COG and BCC/USWM were followed.

The inspection reviewed de-identified data for 40 subjects identified by the review division as the population of interest. The datapoints submitted to the NDA were cross-checked with the ANBL0032 database stored at COG. Data verification was focused on the 12 variables requested by the division as variables of special interest, i.e.:

1. Demographics: Gender, race
2. Birthdate
3. Neuroblastoma diagnostic date
4. ANBL0032 study enrollment date
5. N-myc amplification status
6. Date of start of immunotherapy
7. Date of end of immunotherapy
8. EFS date
9. Type of EFS event
10. Date of death
11. Date last known alive
12. Overall response at end of immunotherapy

The inspection confirms that the data transfer procedures between COG and BCC/US WorldMeds were followed as planned and all data points of interest for the 40 subjects were verifiable and accurate. No discrepancies were noted between ANBL0032 study's data database at COG and the data submitted to the NDA for all 40 subjects of interest.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Michele Fedowitz, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
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Jenn Sellers, M.D. Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
DARRTS: NDA 215500
Review Division/Project Manager/Ashley Lane
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

LEE HONG PAI SCHERF
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MICHELE B FEDOWITZ
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JENN W SELLERS
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215500
Submission Number	5
Submission Date	11/21/2022
Date Consult Received	12/28/2022
Drug Name	eflornithine
Indication	Neuroblastoma
Therapeutic Dose	192 to 768 mg BID depending on BSA for 2 years
Clinical Division	DO2
Protocol Review	Not applicable.

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 12/28/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Sponsor's summary of clinical safety for Study NMTRC014 (SN0005; link);
- Sponsor's clinical study report for Study USWM-FE1-1001 (SN0001; link);
- Sponsor's statistical analysis plan for the ISS (SN0005; link);
- Sponsor's protocol for Study NMTRC014 (SN0001; link);
- Sponsor's protocol for Study USWM-FE1-1001 (SN0001; link);
- Investigator's brochure Version 3.0 (SN0011; link);
- Previous IRT reviews (b) (4)
- Sponsor's Pharmacokinetic Report for Study NMTRC014 (SN0005; link);
- Highlights of clinical pharmacology and cardiac safety (SN0011; link); and
- 120-day safety report (NDA 215500 / eCTD 0030; link).

1 SUMMARY

Eflornithine (DFMO) does not cause a mean increase in the QTc interval ≥ 20 msec at the recommended dose in subjects with normal renal function. – see Table 1 for overall results.

The clinical study NMTRC014 was an open-label, single agent, multicenter, study for patients with high-risk neuroblastoma (HRNB) in remission. Study NMTRC014 evaluated QTc effects in patients with normal renal function receiving the recommended therapeutic doses of eflornithine. The high clinical exposure scenario for eflornithine is not yet known but is likely to be in subjects with renal impairment.

Reference ID: 5146734

Data were analyzed using by-time as the primary analysis, which shows that eflornithine does not cause a mean increase in the QTc interval ≥ 20 msec. (refer to section 4.3). The findings of the primary analysis are further supported by the lack of QTc prolongation in nonclinical data and categorical analysis (section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☒ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• High clinical exposure scenario of eflornithine is not yet known, but is likely to be in patients with impaired renal function as this route accounts for up to 80% of unchanged drug clearance (section 3.1)
• Study NMTRC014 evaluated QTc effects in patients receiving the recommended therapeutic doses of eflornithine.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Visit</th><th>ΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTc</td><td>Eflornithine HCL 500 mg/m2 BID – 1000 mg/m2 BID</td><td>3 hours post dose on Day 1</td><td>4.1</td><td>(2.4 to 5.7)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">Integrated risk assessment not performed.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

IWILFIN did not prolong the QTc interval ≥ 20 msec based on assessment of ECG/PK data from study NMTRC014.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the label submitted to eCTD 0005 (link).

Reference ID: 5146734

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology *IWILFIN does not cause a mean increase in the QTc interval ≥ 20 milliseconds at the approved recommended dose in subjects with normal renal function.*
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

DFMO (Difluoromethylornithine, Eflornithine) is an irreversible inhibitor of enzyme ornithine decarboxylase (ODC) proposed to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent multimodality therapy. The proposed therapeutic dose ranges from 192 to 768 mg BID depending on BSA for 2 years.

Eflornithine has been previously approved in an IV formulation (Ornidyl, approved 1990) for the treatment of trypanosoma brucei gambiense sleeping sickness (NDA 019879) and later as a topical formulation (VANIQA, approved 2000) for the treatment of unwanted facial hair in women (NDA 021145). Both formulations are discontinued, and it is unclear how exposures of the oral formulation compares and if there is sufficient clinical experience as to not require a formal QTc assessment.

The current submission does not include a formal QTc assessment, and we have not previously commented on the QTc assessment plan for this product. ECG/PK data for the new product was only collected in study NMTRC014, which included sparse ECG/PK collection at screening and at 3 h (Tmax ~ 3.5 h) on days 1, 91, and 181 (see appendix 5.1 for additional details). ECG measurements were automatically read. The focus of this review will be on the adequacy of the ECG/PK data from study NMTRC014 to exclude 20 msec mean QTc prolongation using by-time analysis. The ECG/PK collection schedule (pre-dose and Tmax) does not support concentration-QTc analysis.

3.1.1 Clinical pharmacology

See table of highlights of clinical pharmacology and cardiac safety. The proposed dosage eflornithine is based on body surface area as presented in the table below.

Body Surface Area (m^2)	**Dosage**
>1.5	Four tablets orally twice a day (8 tablets or 1,536 mg per day)
0.75 to 1.5	Three tablets orally twice a day (6 tablets or 1,152 mg per day)
0.5 to < 0.75	Two tablets orally twice a day (4 tablets of 768 mg per day)

Reference ID: 5146734

Body Surface Area (m^2)	Dosage
0.25 to < 0.5	One tablet orally twice a day (2 tablets or 384 mg per day)

The drug product is formulated as immediate release oral tablets containing eflornithine hydrochloride (DFMO HCL) 250 mg per tablet (eflornithine free base: 192 mg). Based on the proposed dosage table, most subjects receive DFMO HCL doses between 500 mg/m^2 BID – 1000 mg/m^2 BID. Subjects in study NMTRC014 were dosed according to the dosage table above and the results from the study indicated that steady state exposures were numerically highest in subjects receiving DFMO HCL 750 mg BID compared to those receiving other doses i.e., 250 mg BID, 500 mg BID, or 1000 mg BID (Table 22 of Study NMTRC014 PK report). The 750 mg BID dosage provided geometric mean steady state Cmax (gMean $Cmax_{,ss}$) of ~19 µg/mL while 500 mg BID provided gMean $Cmax_{,ss}$ of ~ 16 µg/mL. Body size (weight, BSA) is the only intrinsic factor known to be associated with eflornithine PK variability. Although renal clearance account for ~80% of unchanged drug clearance, the impact of renal clearance on eflornithine PK is not yet known as no dedicated organ impairment studies have been conducted. As shown in Table 2, study NMTRC014 evaluated QT effects at the anticipated therapeutic exposures. The high clinical exposure scenario for eflornithine is not yet known.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	750 mg BID, oral tablets	~19 µg/mL ($C_{max,ss}$)
Sponsor's High clinical exposure scenario	Not yet known	-
Highest dose in QT assessment	[a]750 mg BID oral tablets	~19 µg/mL
C_{max} Ratio	19 µg/mL / 19 µg/mL = 1	

[a] This was the therapeutic dose associated with the highest exposure in study NMTRC014, a study used for evaluation of QT effects of eflornithine

3.1.2 Nonclinical Safety Pharmacology Assessments

The effects of DFMO on the cardiovascular system were investigated in anesthetized dogs. After IV injection of DFMO at 500 mg/kg to dogs (10 min infusion), a transient decrease in blood pressure (approximately 19%), myocardial contractility (approximately 41%), and heart rate (approximately 10%) were noted (ORNIDYL 1990). There have been no reports of serious adverse effects on the central nervous system nor the respiratory system. DFMO has been safely used clinically for several decades at substantially higher doses than proposed in the current marketing application in the FDA-approved indication for the treatment of African sleeping sickness. Therefore, no additional sponsored pharmacodynamic or safety pharmacology studies have been conducted or were considered warranted by the current Sponsor.

Reference ID: 5146734

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The sponsor evaluated the ΔQTcF effect using descriptive statistics. The number of subjects, mean, and standard deviation are reported. Based on the reported statistics from sponsor's analysis, the maximum upper confidence limit is below 10 msec for the DFMO treatment group. The sponsor's primary analysis for DFMO was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *Reviewer's by-time analysis is evaluated as primary analysis as the cQT analysis is not supported by data from study* NMTRC0*14. The results from the reviewer's analysis show maximum upper confidence limit is below 10 msec for the DFMO treatment group. Please see section 4.3 for details.*

3.2.1.1 Assay Sensitivity

The study was conducted in patients per ICH E14 Q&A 6.1 and therefore no placebo nor moxifloxacin controls were included.

Reviewer's comment: *Assay sensitivity was not established. The QT effects were evaluated to determine if eflornithine excludes large increase.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline). Sponsor didn't report categorical analysis for HR, PR, and QRS.

Reviewer's comment: *Reviewer's analysis results are the same with sponsor's analysis results for QTc. There were 210 subjects who had observed maximum HR above 100 beats/min and one subject experienced QRS >120 msec and 25% increase over baseline in the DFMO treatment group. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor conducted concentration-QT analysis using time matched PK and ECG data collected in study NMTRC014 at baseline and 3-hours post dose on days 1, 91, and 181. The sponsor performed linear regression analysis to assess the relationship between eflornithine concentration and change from baseline in QTcF. According to the sponsor, the slope of the regression line was flat to slightly negative, supporting that there is no apparent QTcF prolongation risk with DFMO treatment at therapeutic levels.

Reviewer's comment: *The reviewer did not conduct concentration-QT analysis as by-time analysis was determined to be a preferable method of QT assessment for this study given the study design and the available PK/ECG time points (See section 4.5).*

Reference ID: 5146734

3.2.4 Safety Analysis

NMTRC014 is an ongoing study, and the safety analysis is based on a cutoff date of June 30, 2021. No deaths have been reported in NMTRC014. Serious AEs were reported in 46 (18%) patients in all strata excluding strata 1b (1500 mg/m^2) and 3 (14%) for patients in strata 1b (5000 mg/m^2). Adverse events led to discontinuation in 13 (5%) in patients in all strata excluding strata 1b and 0 patients in strata 1b. No adverse events belonging to the "Torsade de pointes/QT prolongation" SMQ were reported for NMTRC014. Seizure was reported for two patients (b) (6) and (b) (6)).

No new events included in the "Torsade de pointes/QT prolongation" SMQ or seizure events were reported in the 120-day safety report.

Reviewer's comment: *No other AEs of interest per E14 were reported for the patients who experienced a seizure AE or QTc measurements > 400 msec. The provided datasets provided no additional information about the two seizure events reported.*

4 REVIEWERS' ASSESSMENT

4.1 Evaluation of the QT/RR Correction Method

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG assessments

4.2.1 Overall

Paper ECGs for study NMTRC014 were submitted. Automatic measurements were used for analyses. Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 By-Time Analysis

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG from Study NMTRC014.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The model includes visit day as fixed effect and baseline as a covariate. The model also includes an unstructured covariance matrix to explain the associations among repeated measures within the visit day.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for the DFMO treatment group. The maximum ΔQTcF values are shown in Table 3.

Reference ID: 5146734

Figure 1: Mean and 90% CI of ΔQTcF Time-course (unadjusted CIs).

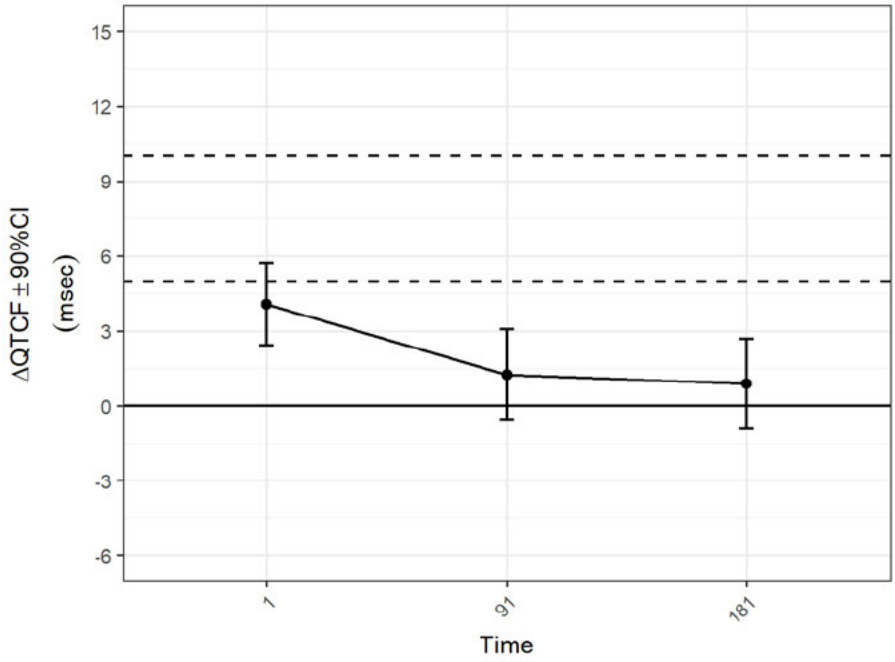


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	N	Time (Hour)	ΔQTCF (msec)	90.0% CI (msec)
DFMO Treatment	1	250	3.0	4.1	(2.4 to 5.7)

4.3.1.1 Assay Sensitivity

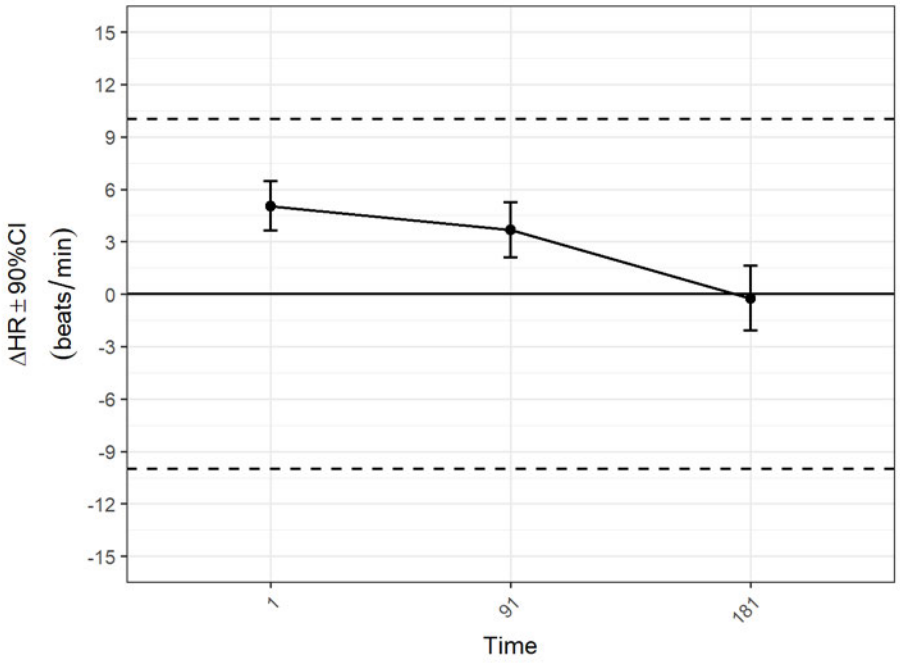
Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for the DFMO treatment group.

Reference ID: 5146734

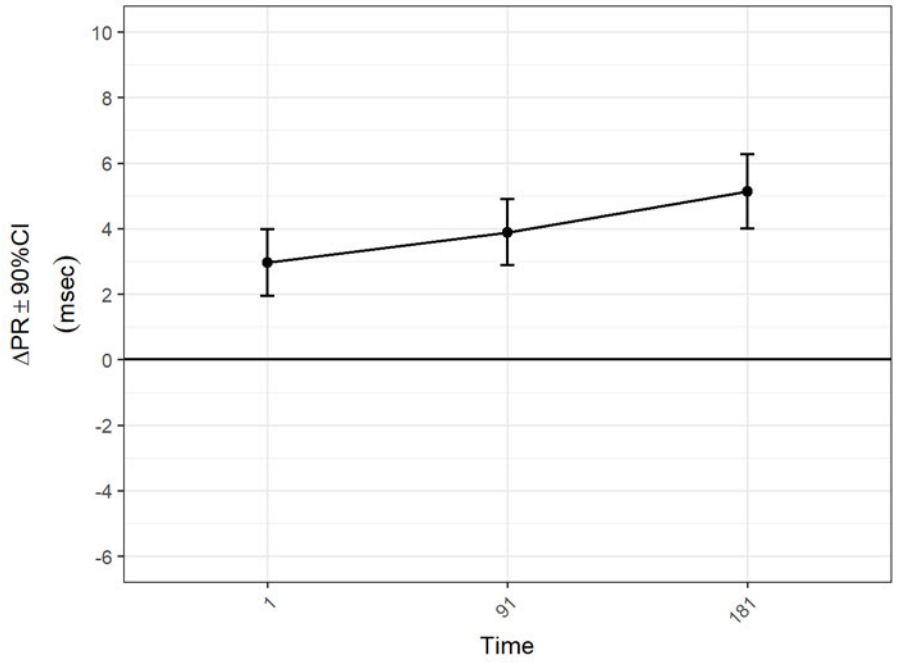
Figure 2: Mean and 90% CI of ΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for the DFMO treatment group.

Figure 3: Mean and 90% CI of ΔPR Time-course

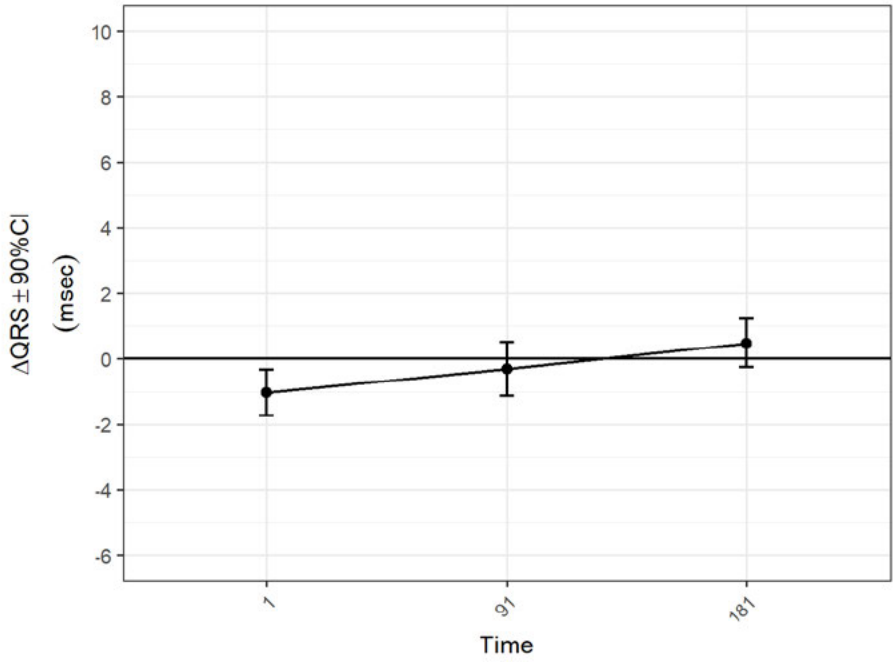


4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for the DFMO treatment group.

Reference ID: 5146734

Figure 4: Mean and 90% CI of ΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs from Study NMTRC014. In the following categorical tables, an omitted category means that no subjects had values in that category. Since the baseline values are missing for some subjects, the number of subjects in categorical analysis is larger than the number of subjects in by-time analysis.

4.4.1 QTc

There were no subjects who had observed QTcF above 480 msec or change from baseline above 60 msec.

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were 210 subjects who had observed maximum HR above 100 beats/min in the DFMO treatment group.

Table 4: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
DFMO Treatment	279	723	69 (24.7%)	297 (41.1%)	210 (75.3%)	426 (58.9%)

Reference ID: 5146734

4.4.3 PR

None of the subjects experienced PR >220 msec in the DFMO treatment group.

4.4.4 QRS

Table 5 lists the categorical analysis results for QRS (≤120 msec, and >120 msec; with and without 25% increase over baseline). There was one subject who had observed QRS >120 msec with 25% increase over baseline in the DFMO treatment group.

Table 5: Categorical Analysis for QRS

Actual Treatment	Total (N)		Value <=120 msec		Value >120 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
DFMO Treatment	258	668	257 (99.6%)	667 (99.9%)	1 (0.4%)	1 (0.1%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Due to the sparseness of the time matched PK and ECG data collected from study NMTRC014, the data was not amenable for linear mixed effect modeling. Therefore, the reviewer did not conduct independent concentration-QTc modeling.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

Reference ID: 5146734

5 APPENDIX

5.1 Evaluation of Clinical QT assessment plan

1. Product Information			
Generic Name	eflornithine	Brand Name	IWILFIN
Drug Class	ornithine decarboxylase inhibitor		
Combination Product	No		
Indication	Neuroblastoma		
Therapeutic Dose	192 to 768 mg BID depending on BSA for 2 years		
Maximum Tolerated Dose	Not studied by Sponsor. Intravenous infusions of up to 200 mg/kg BID are used for treatment of trypanosomiasis		
Dosage Form	Immediate release tablet	Route of Administration	oral

2. QT Studies								
2.1 Primary Studies								
Protocol Number / Population	**ECG Quality**		**Arms**		**Sample Size**		**ECG & PK Assessments**	
	Assessment	**OK?**	**Arms**	**High Dose Covers?**	**No Subjects**	**OK?**	**Timing**	**OK?**
Protocol Number: NMTRC014 Population: Patients Design:	Central Read? No Blinded? No Replicates? Yes	Yes	Highest Dose: 1000 mg/m^2 Placebo: No Positive Control: No	Therapeutic	257 subjects.	Yes	Baseline: Pre-dose baseline Timing: 3 h on days 1, 91 and 181	*Yes*

Reference ID: 5146734

Other								

2.3 Data Pooling	
Data pooling?	No
Did sponsor propose an assessment for heterogeneity?	N/A
Is the data pooling appropriate?	N/A

3. Analysis plan

3.1 Study Objectives Related to QT	
What QTc effect size is the analysis trying to exclude?	20 ms

3.2 Dose Justification

The sponsor has not determined high clinical exposure scenario for eflornithine in patients with neuroblastoma. Organ impairment studies are pending to characterize the impact of renal impairment on PK of eflornithine. The highest tested dose was the maximum proposed therapeutic dose.

3.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No
Primary method for QT correction	QTcF

3.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☐ Other ☒ Not applicable (objective is large mean effects)

3.5 By-Time Analysis	
3.5.1 Investigational Drug	
Primary analysis	No
Did the sponsor use IUT or descriptive statistics?	Descriptive statistics

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For IUT: Does the sponsor use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	N/A
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	N/A
N/A.	
3.5.2 Positive Control	
Primary analysis	N/A
Did the sponsor adjust for multiplicity?	N/A
The study did not include positive control.	
3.6 Exposure-Response Analysis	
3.6.1 Investigational Drug	
Primary analysis	Yes
What is the dependent variable in the sponsor's model?	Single delta
White paper model?	No
Which concentration covariate(s) are included in the model?	Parent
Did the sponsor propose an assessment of delayed effects?	No
Did the sponsor propose an assessment of linearity?	No
Did the sponsor propose model selection criteria?	No
Which methods did the sponsor use for predicting the QT effect?	☐ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
The sponsor did not use the white paper model but rather a simple linear regression analysis. No predictions from the model were made	
3.6.2 Positive Control	
Primary analysis	N/A
Same model as investigational drug	N/A

Reference ID: 5146734

The study did not include positive control			
3.7 Categorical Analysis			
QTcF?	Yes	QRS?	No
ΔQTcF?	Yes	HR?	No
PR?	No	T-wave morphology?	No

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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:	March 7, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215500
Product Name, Dosage Form, and Strength:	Iwilfin (eflornithine) tablets, 192 mg
Applicant/Sponsor Name:	USWM, LLC (dba US WorldMeds)
TTT ID #:	2022-2254
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 27, 2023 for Iwilfin. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Iwilfin (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 CONCLUSION

The Applicant was unable to relocate the statement "IWILFIN (b) (4) as whole tablet, chewed, or crushed & mixed with soft foods or liquids." from the principal display panel on the container label due to insufficient space.[b] However, the Applicant implemented all of our other recommendations and we find the revised container label and carton labeling acceptable from a medication error perspective.

[a] Gao, T. Label and Labeling Review for Iwilfin (NDA 215500). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 Feb 21. TTT ID #: 2022-2254.
[b] NDA 215500 Eflornithine 192 mg/tablet (250 mg as monohydrochloride monohydrate) Sequence Number e0024 Amendment to Original NDA – Response to FDA Information Request received on February 21, 2023. Louisville (KY): USWM, LLC (dba US WorldMeds). 2023 Feb 27. Available from: \\CDSESUB1\EVSPROD\nda215500\0024\m1\us\12-cover-letters\cover-letter-0024-2023-02-27.pdf

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LABEL AND LABELING REVIEW
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)

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

Date of This Review:	February 21, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 215500
Product Name, Dosage Form, and Strength:	Iwilfin (eflornithine) tablets, 192 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	USWM, LLC (dba US WorldMeds)
FDA Received Date:	November 21, 2022, December 22, 2022, and February 1, 2023
TTT ID #:	2022-2254
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

Reference ID: 5129643

1 REASON FOR REVIEW

As part of the approval process for Iwilfin (eflornithine) tablets, the Division of Oncology 2 (DO2) requested that we review the proposed Iwilfin prescribing information (PI), patient package insert, container label, and 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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
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

We reviewed the proposed Iwilfin PI, container label, and carton labeling and determined that they may be improved for clarity.

4 CONCLUSION & RECOMMENDATIONS

The proposed Iwilfin PI, container label, and carton labeling may be improved for clarity. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. To reduce clutter and to improve readability, consider revising Table 1 Dosage Recommendations to the table below for clarity:

Body Surface Area (m^2)	Recommended Dosage
>1.5	768 mg (four tablets) orally twice a day
0.75 to 1.5	576 mg (three tablets) orally twice a day
0.5 to < 0.75	384 mg (two tablets) orally twice a day
0.25 to < 0.5	192 mg (one tablet) orally twice a day

b. As currently presented, the dosage regimen contains (b) (4) . Error prone abbreviations may lead to misinterpretation and medication error. We recommend replacing (b) (4) with the intended meaning, "twice daily".

2. How Supplied/Storage and Handling Section

a. As currently presented, container label states (b) (4) but this information is not mentioned in the proposed Iwilfin PI. Add this storage information to Section 16 How Supplied/Storage and Handling Section for clarity.

b. Clarify the intended meaning of the statement (b) (4) (b) (4)

4.2 RECOMMENDATIONS FOR USWM, LLC (DBA US WORLDMEDS)

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

A. General Comments (Container label & Carton Labeling)

1. Consider removing the statement "IWILFIN (b) (4) chewed, or crushed & mixed with soft foods or liquids." from the principal display panel to reduce clutter.

B. Container Label

1. Relocate the "Rev. mmm/yyyy" below the distributor information to minimize the revision date being confused as the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Iwilfin received on December 22, 2022 from USWM, LLC (dba US WorldMeds), and the listed drug (LD).

Table 2. Relevant Product Information for Iwilfin and the Listed Drug

Product Name	Iwilfin	Ornidyl (NDA 019879)[a]
Initial Approval Date	N/A	11/28/1990
Active Ingredient	eflornithine	eflornithine Hydrochloride
Indication	reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy.	treatment of meningoencephalitic stage of Trypanosoma brucei gambiense infection (sleeping sickness).
Route of Administration	oral	Intravenous
Dosage Form	tablets	For Injection
Strength	192 mg	20,000 mg/100 mL (200 mg/mL)
Dose and Frequency	Iwilfin is taken orally twice daily for two years. The recommended dosage of IWILFIN, based on body surface area (BSA), is provided in table below. **Body Surface Area (m^2) / Dosage** >1.5 — Four tablets orally twice a day (8 tablets or 1,536 mg per day) 0.75 to 1.5 — Three tablets orally twice a day (6 tablets or 1,152 mg per day) 0.5 to < 0.75 — Two tablets orally twice a day (4 tablets of 768 mg per day) 0.25 to < 0.5 — One tablet orally twice a day (2 tablets or 384 mg per day)	100 mg/kg/dose (46 mg/lb/dose) administered every 6 hours by intravenous infusion for 14 days.
How Supplied	Bottle of 100 tablets	Single dose vial
Storage	Store at room temperature, 25°C (77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Store vial at room temperature, preferably below 30°C (86°F). Protect from freezing and light.
Container Closure	White round 100 cc HDPE bottles with an induction seal and (b) (4) cap closure. Each bottle contains	Vial

[a] Ornidyl [Prescribing Information]. Bridgewater (NJ): sanofi-aventis U.S. LLC. 2014 Jan 24. Available from: \\CDSESUB1\EVSPROD\nda019879\0012\m1\us\pi.pdf.

	5 grams of silica gel desiccant packaged in a (b) (4) sachet with (b) (4) coil filler.	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 29, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, eflornithine. Our search only identified previous reviews for Eflornithine Hydrochoride Cream, 13.9% (NDA 021145), and [redacted]. We considered our previous recommendations for [redacted] to see if they are applicable for this current review.

[redacted]

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,[c] along with postmarket medication error data, we reviewed the following Iwilfin labels and labeling submitted by USWM, LLC (dba US WorldMeds).

- Container label received on November 21, 2022
- Carton labeling received on November 21, 2022
- Prescribing Information (Image not shown) received on February 1, 2023, available from \\CDSESUB1\EVSPROD\nda215500\0018\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean.docx
- Patient Package Insert received on December 22, 2022, available from \\CDSESUB1\EVSPROD\nda215500\0009\m1\us\114-labeling\draft\labeling\iwilfin-ppi_track-changes.docx.

G.2 Label and Labeling Images

Container label

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

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