CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208901Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 26, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 208901
Product Name and Strength:	Tolsura (itraconazole) Capsules, 65 mg
Applicant/Sponsor Name:	Mayne Pharma International Pty Ltd.
FDA Received Date:	October 25, 2018
OSE RCM #:	2018-397-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

Division of Anti-Infective Products (DAIP) requested that we review the revised container labels for Tolsura (itraconazole) Capsules, 65 mg (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review (also see Appendix B).[a]

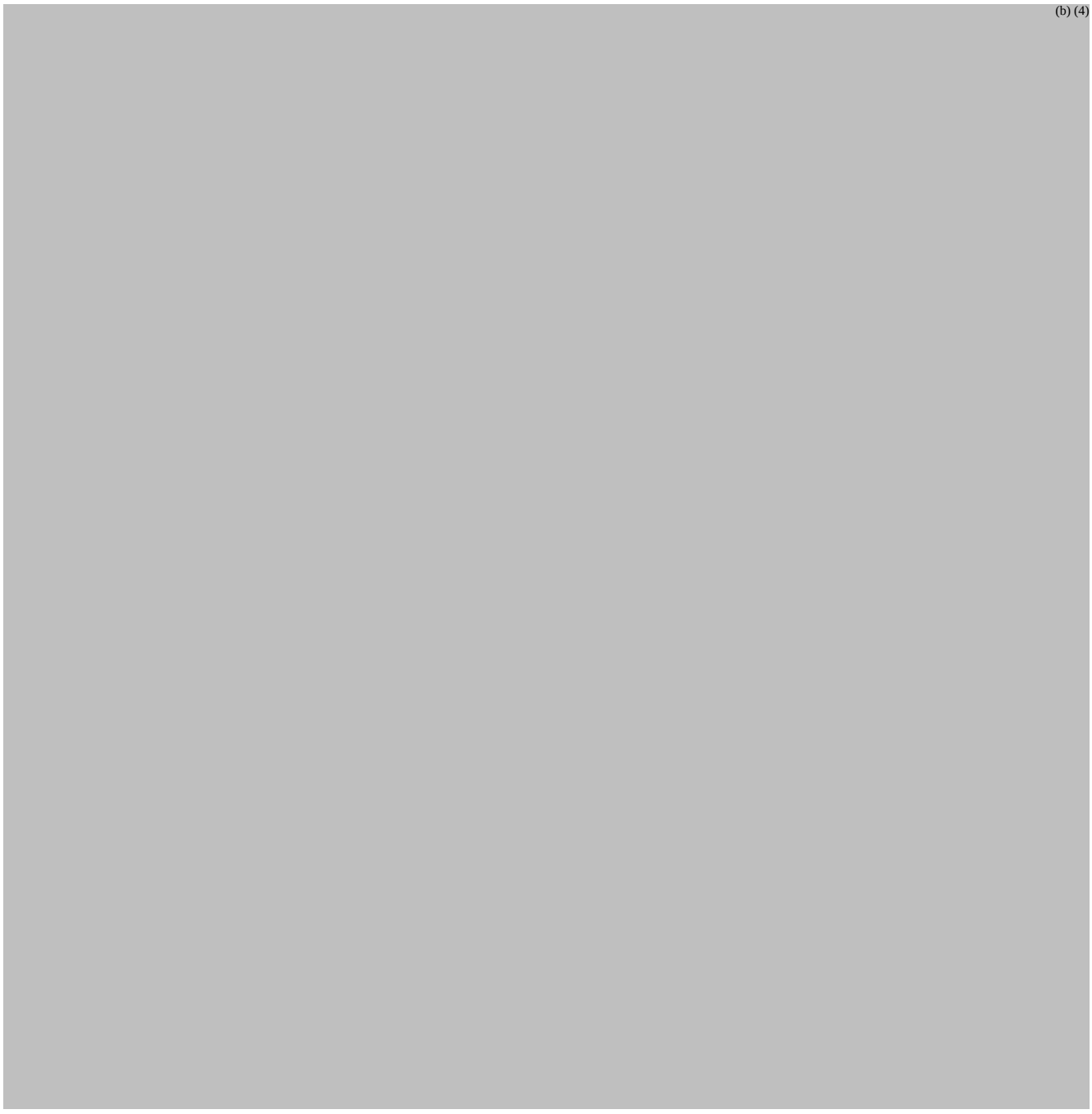
2 CONCLUSION

The revised container labels for Tolsura (itraconazole) Capsules are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Myers, D. Label and Labeling Review for Tolsura (itraconazole) NDA 208901. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 04. RCM No.: 2018-397.

APPENDIX A. IMAGES OF LABELS RECEIVED ON OCTOBER 25, 2018

Container labels



APPENDIX B. RESPONSE TO REQUEST FOR SUBMISSION OF EXPIRATION DATE FORMAT

In addition to the images above, Mayne supplied the following information within their Cover Letter, dated October 25, 2018, regarding the proposed format of "MMMYYYY" for the expiration date[b]:

1. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. For the format of the expiration date, we recommend using a format like [examples provided].

Response

The sample and trade labels have been updated in accordance with the above recommendations. An example of format used for the expiry date and serialisation details is provided below. The expiry date will be printed as MMMYYYY, which is consistent with the FDA's recommendation.

[b] Full communication available at the following link \\cdsesub1\evsprod\nda208901\0021\m1\us\12-cover-letters\cover-letter-ir-response-25oct2018.pdf

---

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
10/26/2018

OTTO L TOWNSEND
10/26/2018

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:	October 24, 2018
To:	Sumathi Nambiar, MD, MPH Director **Division of Anti-Infective Products (DAIP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** David Foss, Pharm. D., MPH, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TOLSURA (itraconazole capsules)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 208901
Applicant:	Mayne Pharma Inc, Authorized U.S. Agent for Mayne Pharma International Pty Ltd

1 INTRODUCTION

On February 16, 2018, Mayne Pharma Inc, Authorized U.S. Agent for Mayne Pharma International Pty Ltd, resubmitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 208901 for TOLSURA (itraconazole capsules). The Reference Listed Drug (RLD) is NDA 020083, SPORANOX (itraconazole) Capsules, held by Janssen Pharmaceuticals, Inc. This resubmission is in response to a Refuse to File (RTF) letter issued by the Division of Anti-Infective Products (DAIP) to Mayne Pharma Inc, Authorized U.S. Agent for Mayne Pharma International Pty Ltd, dated January 29, 2016 to the Applicant's November 30, 2015 original submission for NDA 208901.

The proposed indication for TOLSURA (itraconazole capsules) is for the treatment of the following fungal infections in immunocompromised and non-immunocompromised adult patients:

1. Blastomycosis, pulmonary and extrapulmonary
2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and
3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B 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 requests by the Division of Anti-Infective Products (DAIP) on April 4, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TOLSURA (itraconazole capsules).

2 MATERIAL REVIEWED

- Draft TOLSURA (itraconazole capsules) PPI received on February 16, 2018 and received by DMPP and OPDP on October 15, 2018.
- Draft TOLSURA (itraconazole capsules) Prescribing Information (PI) received on February 16, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 15, 2018.
- Approved SPORANOX (itraconazole) comparator labeling dated May 8, 2018.

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 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)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

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.

7 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/

KAREN M DOWDY
10/24/2018

DAVID F FOSS
10/25/2018

MARCIA B WILLIAMS
10/25/2018

LASHAWN M GRIFFITHS
10/25/2018

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

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

Memorandum

Date: October 18, 2018

To: Alma Davidson
Division of Anti-Infective Products (DAIP)

Alison Rodgers, Regulatory Project Manager, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TOLSURA (itraconazole capsules) for Oral use

NDA: 208901

In response to DAIP's consult request dated April 4, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Tolsura.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAIP on October 15, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAIP on October 16, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

47 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/

DAVID F FOSS
10/18/2018

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	October 4, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 208901
Product Name and Strength:	Tolsura (itraconazole) Capsules, 65 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mayne Pharma International Pty Ltd.
FDA Received Date:	February 16, 2018 and September 24, 2018
OSE RCM #:	2018-397
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

This review evaluates the proposed container labels and prescribing information for Tolsura (itraconazole) Capsules, 65 mg (NDA 208901) to identify areas of vulnerability that may lead to medication errors. The Division of Anti-Infective Products (DAIP) requested this review as part of their evaluation of the 505(b)(2) submission for Tolsura (itraconazole) Capsules, 65 mg. The listed product (Sporanox (itraconazole) Capsules, 100 mg (NDA 020083)) was approved September 11, 1992.

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
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted container labels and prescribing information, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information (FPI), Section 2, *Dosage and Administration*			

1. As currently presented the text regarding dosing regimen may be difficult to understand. Since the dosing regimen information is complex, we recommend that a table might be a better manner to communicate this information (see example below):

Table 1: Dosage and Administration	
	Daily Dosing
Treatment of Blastomycosis and Histoplasmosis	
Recommended dose	130 mg (2 x 65 mg capsules) once daily
If no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 65-mg increments to a maximum of 260 mg/day. Doses above 130 mg/day should be given in two divided doses.	(b) (4)
Treatment of Aspergillosis	
Recommended (b) (4) dose (b) (4)	130 mg (2 x 65 mg capsules) once daily
	(b) (4)
	260 mg/day (130 mg (2 x 65 mg capsules) twice daily)
Treatment in Life-Threatening Situations	
Although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose should be used.	A loading dose of 130 mg (2 x 65 mg capsules) three times daily (390 mg/day) is recommended to be given for the first 3 days, followed by the appropriate recommended dosing based on indication. Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

(b) (4)

(b) (4)			
FPI, Section 3, *Dosage Forms and Strengths*			
1.	As currently presented, we note the inclusion of (b) (4)	Per 21 CFR 201.57(c)(4)(i) and 21 CFR 201.57(c)(4)(ii) the (b) (4) is not necessary for inclusion in Section 3.	We recommend deletion of (b) (4)
FPI, Section 16, *How Supplied/Storage and Handling*			

1.	We note the inclusion of information on the [redacted] (b) (4)	Only products for sale should be listed in this section as required by 21 CFR 201.57(c)(17)(ii).	Remove the information on [redacted] (b) (4)
2.	As currently presented the storage statement includes "Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light resistant container (USP)."	The degree symbol (°) and units of temperature measurement (Centigrade and Fahrenheit) following the first numbers in the temperature ranges (e.g., the degree and Centigrade symbols (°C) following the 15 and the degree and Fahrenheit symbols (°F) following the 59) are missing.	Add the degree and Centigrade symbols (°C) following the 15 and degree and Fahrenheit symbols (°F) following the 59 within the storage information to provide clarity. To provide further clarity, consider replacing the hyphens with their intended meaning "to." For example, "…excursions permitted to 15°C to 30°C (59°F to 86°F)…"

Table 3: Identified Issues and Recommendations for Mayne Pharma International Pty Ltd. (entire table to be conveyed to Applicant)

Container Labels (trade and sample)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, there is no statement included on the principal display panel (PDP) to alert dispensers that Tolsura is not [redacted] (b) (4) on a mg per mg basis with other formulations of itraconazole.	Because of differing bioavailability, substitution of Tolsura with other itraconazole formulations on a mg per mg basis can result in wrong strength medication errors.	To reduce the risk of wrong strength medication errors we recommend adding the statement, "Attention: Tolsura is NOT interchangeable on a mg per mg basis with other formulations of itraconazole." to the principal display panel. In addition, we recommend bolding the font, changing the color of the font, surrounding this information with a box, and/or highlighting the information to draw attention

			to this important information (see example below): **Attention: Tolsura is NOT interchangeable on a mg per mg basis with other formulations of itraconazole.**
Container Label (trade)			
1.	As currently presented there is no space notated for the product lot number and expiration date.	The lot number statement is required on the immediate container label per 21 CFR 201.10(i)(1) and the product expiration date is also required on the immediate container label per 21 CFR 201.17.	Include the space notation for the lot number statement and expiration date. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number/expiration date that can be mistaken as the lot number/expiration date. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. For the format of the expiration date, we recommend using a format like either: DDMMMYYYY (e.g., 31JAN2013) MMMYYYY (e.g., JAN2013) YYYY-MMM-DD (e.g., 2013-JAN-31) YYYY-MM-DD (e.g., 2013-01-31)
2.	As currently presented the storage statement includes "Store at 25°C	The degree symbol (°) and units of temperature measurement (Centigrade	Add the degree and Centigrade symbols (°C) following the 15 and degree

	(77°F); excursions permitted 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light resistant container (USP)."	and Fahrenheit) following the first numbers in the temperature ranges (e.g., the degree and Centigrade symbols (°C) following the 15 and the degree and Fahrenheit symbols (°F) following the 59) are missing.	and Fahrenheit symbols (°F) following the 59 within the storage information to provide clarity. To provide further clarity, consider replacing the hyphens with their intended meaning "to." For example, "…excursions permitted to 15°C to 30°C (59°F to 86°F)…"
Container Label (sample)			
1.	As currently presented, the format for the expiration date is not defined.	The use of abbreviations within the expiration date can result in confusion regarding the actual expiration date leading to deteriorated drug medication errors.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. For the format of the expiration date, we recommend using a format like either: DDMMMYYYY (e.g., 31JAN2013) MMMYYYY (e.g., JAN2013) YYYY-MMM-DD (e.g., 2013-JAN-31) YYYY-MM-DD (e.g., 2013-01-31)

4 CONCLUSION

Our evaluation of the proposed container labels and prescribing information identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Mayne Pharma International Pty Ltd. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Tolsura that Mayne Pharma International Pty Ltd. submitted on September 25, 2018, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Tolsura		
Product Name	Sporanox (NDA 020083)	Tolsura
Initial Approval Date	September 11, 1992	N/A
Active Ingredient	itraconazole	itraconazole
Indication	Treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: 1. Blastomycosis, pulmonary and extrapulmonary 2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and 3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy. Sporanox capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients: 1. Onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium), and 2. Onychomycosis of the fingernail due to dermatophytes (tinea unguium).	Treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: 1. Blastomycosis, pulmonary and extrapulmonary 2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and 3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

	Prior to initiating [redacted], appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.	
Route of Administration	oral	oral
Dosage Form	capsule	capsule
Strength	100 mg	65 mg
Dose and Frequency	Sporanox capsules should be taken with a full meal to ensure maximal absorption. Sporanox capsules must be swallowed whole. Sporanox capsules is a different preparation than Sporanox Oral Solution and should not be used interchangeably. <u>Treatment of Blastomycosis and Histoplasmosis</u>: The recommended dose is 200 mg once daily (2 capsules). If there is no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 100-mg increments to a maximum of 400 mg daily. Doses above 200 mg/day should be given in two divided doses. <u>Treatment of Aspergillosis</u>: A daily dose of 200 to 400 mg is recommended. <u>Treatment of Aspergillosis</u>: A daily dose of 200 to 400 mg is recommended.	[redacted] Tolsura capsules must be swallowed whole. <u>Treatment of Blastomycosis and Histoplasmosis</u>: The recommended dose is 130 mg once daily (2 x 65 mg capsules). If [redacted] no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 65-mg increments to a maximum of 260 mg [redacted]. Doses above 130 mg/day

	Treatment in Life-Threatening Situations: In life-threatening situations, a loading dose should be used. Although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose of 200 mg (2 capsules) three times daily (600 mg/day) be given for the 3 days of treatment. Treatment should be continued for a minimum of three months and until clinical parameters and laboratory test indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Sporanox capsules and oral solution should not be used interchangeably. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis. Treatment of Onychomycosis: Toenails with or without fingernail involvement: The recommended dose is 200 mg (2 capsules) once daily for 12 consecutive weeks.	should be given in two divided doses. Treatment of Aspergillosis: (b) (4) Treatment in Life-Threatening Situations: (b) (4) Although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, (b) (4) a loading dose of 130 mg (2 x 65 mg capsules) three times daily (390 mg/day) be given for the first 3 days (b) (4) Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

	Treatment of Onychomycosis: Fingernails only: The recommended dosing regimen is 2 treatment pulses, each consisting of 200 mg (2 capsules) b.i.d. (400 mg/day) for 1 week. The pulses are separated by a 3-week period without Sporanox.	
How Supplied	Unit-dose blister packs of 3 x 10 capsules Bottles of 30 capsules *Pulse*Pak® containing 7 blister packs x 4 capsules	Trade: Bottles of 60 capsules. (b) (4)
Storage	Store at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.	Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light resistant container (USP).
Container Closure		The 60-count trade pack is packaged in a 75 cc HDPE bottles with induction foil seal and (b) (4) caps. The 8-count sample pack is packaged in a 30 cc HDPE bottles with induction foil seal and (b) (4) caps.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 1, 2018, we searched the L:drive and AIMS using the terms, Tolsura and itraconazole to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified four previous reviews[a,b,c,d], that we reviewed and determined that the previous reviews identified are not applicable to this current review.

[a] Myers, D. Proprietary Name Review for Tolsura (itraconazole) NDA 208901. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 14. RCM No.: 2018-21597895.

[b] Kolejian, S. Proprietary Name Review for (b) (4) (itraconazole) NDA 208901. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 17. RCM No.:2015-2259330.

[c] Mena-Grillasca, C. Label and Labeling Review for Onmel (itraconazole) NDA 022484. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 DEC 28. RCM No.: 2010-882.

[d] Hamilton-Stokes, D. Medication Error Post-Marketing Safety Review Memo for Itraconazole NDA 020083. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2007 MAR 02. RCM No.: 2007 MAR 02.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels 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 Tolsura labels and labeling submitted by Mayne Pharma International Pty Ltd. on February 16, 2018 and September 24, 2018.

- Container label (received on February 16, 2018)
- Prescribing Information (received on September 24, 2018) available at the following link: \\cdsesub1\evsprod\nda208901\0018\m1\us\114-labeling\draft\labeling\proposed-labeling-text-word.docx

F.2 Label and Labeling Images

(b) (4)

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

[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
10/04/2018

OTTO L TOWNSEND
10/04/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric 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

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 09-19-2018 **Date consulted:**4-13-2018

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara N. Johnson, M.D., M.S.
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Anti-infective Products

Drug: Tolsura (itraconazole) capsules; NDA 208901

Applicant: Mayne Pharma Inc.

Proposed Indication: Treatment of fungal infections in immunocompromised and non-immunocompromised patients

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Labeling submitted as part of 505b2 application

Materials Reviewed:
- Applicant's proposed labeling and supporting safety review
- Approved Sporanox labeling (5-8-2018) (Reference Listed Drug)
- Literature review

Consult Question: Please review the Pregnancy and Lactation Labeling Rule (PLLR) Labeling

INTRODUCTION

The applicant submitted a 505b2 application for Tolsura (itraconazole) capsules on 2-16-2018, for a proposed indication of treatment of fungal infections in immunocompromised and non-immunocompromised patients. The Division of Anti-Infective Products (DAIP) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

The reference listed drug (RLD) Sporanox (NDA 20083) 100 mg capsule, manufactured by Janssen, was approved in 1992. Approved indications include the following fungal infections:

- Blastomycosis, pulmonary and extrapulmonary
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Sporanox is also approved for the treatment of onychomycosis of the toenail and fingernail due to dermatophytes (tinea unguium).

The applicant has been marketing itraconazole 50 mg capsules in the European Union and Australia since 2014. Tolsura drug characteristics include the following:

- Proposed indications: same as the RLD, excluding treatment of onychomycosis
- 65 mg capsule
- half-life 34-42 hours; 15 days to achieve steady state
- molecular weight 705.64 Daltons
- serious adverse reactions include
    - rare cases of serious hepatotoxicity, including liver failure and death.

<u>Systemic Fungal Infections in Pregnancy</u>
Systemic fungal infections in pregnancy are rare and may be associated with

immunocompromised conditions such as HIV infection[1], or may occur in the general population.[2,3,4] These infections may require prolonged duration of treatment (months).[5,6]

Current state of the labeling of RLD, Sporanox (5-8-2018)

Currently approved Sporanox labeling is not in the Physician Labeling Rule (PLR) format. The following pregnancy and lactation information is included in currently approved Sporanox labeling:

Pregnancy (previously category C)

- Human data: case reports of congenital abnormalities (cross reference to Post-Marketing Experience):
    - skeletal, genitourinary tract, cardiovascular and ophthalmic malformations, chromosomal and multiple malformations
- Animal reproduction studies that showed maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 5-20 times the maximum recommended human dose (MRHD)
- A statement that itraconazole should be used during pregnancy only if the potential benefits justify the potential risks to the fetus
- A statement that itraconazole should not be used for the treatment of onychomycosis in women who are pregnant or contemplating pregnancy
    - Contraception recommendations throughout therapy and for 2 months following the end of treatment.

---

[1] Centers for Disease Control and Prevention Webpage People living with HIV/AIDS https://www.cdc.gov/fungal/infections/hiv-aids html

[2] Baker T, Patel A, Halteh P, et al. Blastomycosis during pregnancy: a case report and review of the literature. Diagnostic Microbiology and Infectious Disease 88 (2017) 145-151.

[3] Whitt SP, Koch GA, Fender B, et al. Histoplasmosis in Pregnancy. Arch Inter Med 2004:164:454-458.

[4] Kruetzelmann A, Sobottka I, Fiehler J, et al. Relapsing cerebral aspergilloma associated with pregnancy. Clinical Neurology and Neurosurgery 115 (2013) 1154-1156.

[5] Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 2008; 46:1801.

[6] Wheat LJ, Freifeld AG, Kleiman MB et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Infectious Diseases Society of America Clin Infect Dis. 2007;45(7):807.

Nursing Mothers

- A statement that itraconazole is excreted in human milk
- A statement to weigh the benefits of therapy with the potential risks to the infant
- A statement that the Centers for Disease Control and Prevention advise HIV-infected women not to breastfeed to avoid potential transmission of HIV to uninfected infants.

REVIEW OF DATA

Pregnancy

Nonclinical Experience

No additional reproductive and developmental nonclinical studies were conducted for this submission. Please refer to the FDA PLLR Nonclinical review by Dr. Owen McMaster.

Review of Human Pregnancy Data

Applicant's literature review

The applicant's review of the published literature included two observational studies, reviewed below, and summarized in Appendix I.

1. A prospective observational cohort study conducted by a teratology information service in Italy showed no increase in major birth defects in 206 women exposed to itraconazole in the first trimester compared with 207 unexposed pregnant women.[7] The risk for spontaneous abortion was higher than that seen in the itraconazole exposed group (11.2% compared to 4.8%, $p<0.05$). Outcomes were based on patient reports. The authors note that they cannot exclude that there may have been some false reporting in that some women who had a pregnancy termination may have reported them as a spontaneous abortion. The mean daily dose was 182 mg$\pm$63 mg, and the mean treatment duration was 6.9 days$\pm$6.4 days. The gestational age at enrollment was not significantly different in the two groups (gestational age at enrollment not reported in the publication).

Reviewer Comments

The reliability of the higher spontaneous abortion rate is questionable, as outcomes were not medically confirmed. Additionally, although the spontaneous abortion rate was higher in the itraconazole exposed group compared to the unexposed group, it is still lower than the background rate of 15-20% in the general population.

[7] DeSantis M, Di Gianantonio E, Cesari E, Ambrosini G, Staface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome. Drug Saf 2009;32(3):239-244.

2. A prospective observational cohort study showed no increase in major birth defects in 198 women exposed to itraconazole in the first trimester compared with 198 unexposed pregnant women.[8] The risk for spontaneous abortion in the itraconazole exposed group was higher when compared to the unexposed group (12.6% vs. 4%) (RR 1.75, 95% CI 1.47-2.09). The median daily dose was 200 mg, and the mean treatment duration was 8.5 days. Outcomes were based on physician reports.

   The authors note that the unexposed group of women enrolled into the study later than the exposed group (timing of enrollment for each group not reported in the publication), and that this difference may have accounted for the difference in the spontaneous abortion rate.

Reviewer Comments

DPMH concurs with the authors' assessment that the difference in spontaneous abortion rate may be due to left truncation bias due to differences in gestational timing of enrollment.[9] Additionally, although the spontaneous abortion rate was higher in the itraconazole exposed group compared to the unexposed group, it is still lower than the background rate of 15-20% in the general population.

DPMH Literature Review

DPMH performed a search of published literature on itraconazole exposure in pregnancy, and identified two additional publications, reviewed below (see summary table in Appendix I).

1. A retrospective cohort study that used Danish birth records and National Prescription data of 687 women exposed to itraconazole in the first trimester compared to 968,236 unexposed pregnant women, showed no increase in the rate of major birth defects overall.[10] Only outpatient dispensings were available. Only live births were assessed; infants with chromosomal abnormalities and genetic syndromes were excluded. The cumulative dose exposure in the first trimester was 400 mg among 58% of the exposed cohort.

2. A retrospective cohort study that used Danish birth records and National Prescription data of 131 women exposed to itraconazole in week 7 through 22 compared to 524 unexposed pregnant women showed no increase in the rate of spontaneous abortion (defined as

---

[8] Bar-Oz B, Moretti ME, Bishai R, Mareels G, Van Tittelboom T, Verspeelt J, Koren G. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. Am J Obstet Gynecol 2000; 183:617-20.

[9] Margulis, AV, Mittleman MA, Glynn RJ, Holmes LB, and Hernández-Díaz S, 2015, Effects of Gestational Age at Enrollment in Pregnancy Exposure Registries, Pharmacoepidemiol Drug Saf, Apr 24(4):343–352.

[10] Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med. 2013 Aug 29;369(9):830-9.

pregnancy loss from 7 through 22 gestational weeks).[11] Only outpatient dispensings were available.

Reviewer Comments

Limitations of the studies include the lack of outcome data on prolonged exposure in pregnancy, and treatment during hospitalization.

Review of Pharmacovigilance Database

The applicant's global safety database (cut-off date 7-18-2018) included one pregnancy report following exposure to itraconazole 400 mg for treatment of vaginal candidiasis in the first trimester. The case report consisted of a major malformation reported as sirenomelia; no additional information was available.

Discussion and Conclusion

There are no data on exposure during pregnancy for the approved systemic fungal infections. Available data from three published studies on itraconazole exposure (sample size 198-687) during pregnancy have shown no increased risk of major birth defects overall. However, these studies are based on short courses of treatment, and may underestimate the risk for prolonged exposure due to a longer course of treatment.

Available published data on the risk of spontaneous abortion are conflicting and may be subject to bias due to earlier gestational timing of enrollment and residual confounding in the exposed group compared to the unexposed group.

Therefore, it is appropriate to include risk summary statements in the Pregnancy subsection of labeling that reflect these conclusions, and a summary of the data and limitations under the Human Data heading.

DPMH agrees with the applicant's proposal to not include contraception recommendations, as there is no identified safety signal in pregnancy based on available data.

Lactation

Nonclinical Experience

No additional nonclinical studies were submitted with this submission.

[11] Molgaard-Nielsen D, Svanstrom H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and still birth. JAMA 2016;315(1):58-67.

Review of Human Lactation Data

Applicant's Literature Review

The applicant did not identify any publications in the literature.

DPMH Literature Review

DPMH conducted a search of the published literature, *Medications and Mothers' Milk*[12], and the Drugs and Lactation Database (LactMed)[13]. DPMH identified a published report that estimates a relative infant dose of 1.48% based on unpublished data from 2 healthy volunteers who were administered two oral doses of itraconazole 200 mg 12 hours apart. The source of data is a personal communication between Janssen Pharmaceuticals and Gerald Briggs in 1996.[14] Milk samples were obtained with a breast pump at 4, 24, and 48 hours after the second dose. The average milk concentrations of itraconazole were 70.2, 27.7, and 16.2 mcg/L, respectively. At 72 hours, the milk level was 20.1 mcg/L in one woman and not detectable (<5 mcg/L) in the other. Because milk sampling was not performed at steady state (approved Sporanox labeling states that it takes 15 days to achieve steady state), Gerald Briggs notes that these milk levels underestimate the amount of itraconazole in breastmilk, and recommends that "women taking itraconazole should probably not breastfeed".[12]

Medications and Mother's Milk states that based on "limited data, probably compatible" with breastfeeding. LactMed recommends that "Until more data become available, an alternate drug may be preferred, especially while nursing a newborn or preterm infant".

Review of Pharmacovigilance Database

The applicant performed a review of their pharmacovigilance safety database for cases of itraconazole and lactation and did not identify any reports.

Discussion and Conclusion

There is no new data beyond the 1996 data that supported the statement in approved labeling of the RLD, which states that itraconazole is excreted in human milk. These data are based on administration of 2 doses of itraconazole in 2 women. The study results are not informative, as

[12] Hale, Thomas (2018) Medications and Mothers' Milk online

[13] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database that reviews available information on drug levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[14] Personal Communication between Gerald Griggs and Janssen Pharmaceutical 1996 in Briggs Drug in Pregnancy and Lactation online 2018 https://online.lexi.com/lco/action/doc/retrieve/docid/1090/5711614

the study was not conducted at steady state, which takes 15 days to achieve. Available data are limited and may underestimate the amount of itraconazole in breast milk; therefore, these data should not be included in labeling. There is no information on the effects of itraconazole on breastfed infants or on milk production. In the absence of data and serious safety concerns, it is reasonable to include the PLLR benefit-risk statement. DPMH and DAIP discussed whether it would be helpful to include a statement to consider pumping and discarding milk during treatment and for 9-11 days after the last dose (5-6 times the half-life) for women receiving a short course of treatment. DAIP felt that this type of statement would not be applicable as most patients would be receiving itraconazole for several months.

Females and Males of Reproductive Potential

Nonclinical Experience

The RLD labeling includes nonclinical data that showed no adverse effects on fertility at 5 times the MRHD. No additional nonclinical studies were submitted with this application.

Review of Human Infertility Data

Applicant's Literature Review

The applicant did not identify any published human data on infertility effects following exposure to itraconazole.

DPMH Literature Review

DPMH performed a search of published literature on itraconazole and infertility and did not identify any publications.

Review of Pharmacovigilance Database

The applicant performed a review of their pharmacovigilance safety database for cases of itraconazole and infertility and did not identify any cases.

Discussion and Conclusion

Animal studies of administration of itraconazole showed no adverse effects on fertility, and there are no human data. Therefore, subsection 8.3, Females and Males of Reproductive Potential, will not be included in labeling.

DPMH LABELING RECOMMENDATIONS

The Pregnancy and Lactation subsections of Tolsura labeling were structured to be consistent with the PLLR. DPMH has the following recommendations for the Tolsura labeling:

- **8.1 Pregnancy**
    - The "Pregnancy" subsection of Tolsura labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" sections.

- **8.2 Lactation**
    - The "Lactation" subsection of Tolsura labeling was formatted in the PLLR format to include the "Risk Summary" section.

DPMH recommendations are below and reflect the discussions with DAIP on 9-18-2018. **See final labeling for all of the labeling revisions negotiated with the applicant.**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on exposure to itraconazole during pregnancy for the approved indications. Published epidemiologic studies of women exposed to short courses of treatment with itraconazole in the first trimester of pregnancy have reported no risk of major birth defects overall and inconclusive findings on the risk of miscarriage *(see Data)*.

In animal reproduction studies, itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately (b) (4)- (b) (4) times the maximum recommended human dose (MRHD), and in mice at dosage levels of approximately (b) (4) times the MRHD *(see Data)*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Published prospective and retrospective cohort studies of women exposed to short courses of treatment with itraconazole in the first trimester of pregnancy (sample size 198-687) have reported no increase in the rate of major birth defects. The most important methodological limitation of these studies is the short duration of exposure (mean duration 6.9 to 8.5 days), or the lack of information on treatment duration. The risk of prolonged exposure in pregnancy is not known.

Published prospective and retrospective cohort studies of pregnant women exposed to itraconazole (sample size 131-198) have reported inconsistent findings on the risk of miscarriage. Available data are inconclusive and limited by possible bias due to earlier enrollment and possible residual confounding in the exposed group compared to the unexposed group.

Animal Data

Itraconazole has been shown to cross the placenta in a rat model. In animal reproduction studies, itraconazole administration to rats and mice during organogenesis resulted in maternal toxicity, embryotoxicity and teratogenicity at and above 40 and 80 mg/kg respectively (doses equivalent to (b) (4) and (b) (4)-times the maximum recommended human dose of (b) (4) mg/day). In (b) (4) the

teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

8.2 Lactation

Risk Summary

Itraconazole is (b) (4) in human milk; however, there are no data on the amount of itraconazole in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TOLSURA and any potential adverse effects on the breastfed child from TOLSURA or from the underlying maternal condition.

17. PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy *[see Use in Specific Populations (8.1)]*.

Appendix I

Table 1 Summary of Published Studies on Itraconazole and Major Birth Defects and Spontaneous Abortion (SAB)

Study	Number exposed in the first trimester	Comparator number (unexposed)	Findings	Comments
2016 Denmark Retrospective cohort study based on data from the Danish Medical Birth Register[15]	131	524	• No increase in the risk for SAB	• No dose information reported
2013 Denmark Retrospective cohort study based on data from the Danish Medical Birth Register[16]	687	968,236	• No increase in the risk for major birth defects overall	The cumulative dose exposure in the first trimester was 400 mg among 58% of the exposed cohort.

[15] Molgaard-Nielsen D, Svanstrom H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and still birth. JAMA 2016; 315(1):58-67.

[16] Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med. 2013 Aug 29;369 (9):830-9.

Study	Number exposed in the first trimester	Comparator number (unexposed)	Findings	Comments
2009 Italy Teratogen Information Service[17]	206	207	• No increase in the risk for major birth defects overall • Increased risk for SAB (11.8% vs. 4.8%, p<0.05)	• The mean daily dose was 182 mg±63 mg, and the mean treatment duration was 6.9 days±6.4 days. • SAB rate still lower than background rate in general population
2000 Canada Prospective observational cohort study[18]	198	198	• No increase in the risk for major birth defects overall • Increased risk for SAB (12.6% vs. 4%) (RR 1.75, 95% CI 1.47-2.09).	• The median daily dose was 200 mg, and the mean treatment duration was 8.5 days • Possible bias due to earlier enrollment in exposed group; SAB rate still lower than background rate in general population

[17] DeSantis M, Di Gianantonio E, Cesari E, Ambrosini G, Staface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome. Drug Saf 2009; 32(3):239-244.

[18] Bar-Oz B, Moretti ME, Bishai R, Mareels G, Van Tittelboom T, Verspeelt J, Koren G. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. Am J Obstet Gynecol 2000; 183:617-20.

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/

LEYLA SAHIN
09/19/2018

TAMARA N JOHNSON
09/20/2018

LYNNE P YAO
09/26/2018