CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210850Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 21, 2022
Requesting Office or Division:	Division of Gastroenterology
Application Type and Number:	NDA 210850
Product Name and Strength:	Sincalide for Injection 5 mcg/vial
Submission date:	November 21, 2022
Applicant/Sponsor Name:	MAIA Pharmaceuticals Inc. (MAIA)
TTT ID#	2022-2110-2
DMEPA 1 Primary Reviewer:	Sherly Abraham, RPh
DMEPA 1 Team Leader:	Idalia Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 21, 2022 for Sincalide for Injection. Division of Gastroenterology (DG) requested that we review the revised label and labeling for Sincalide for Injection (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 implemented all of our recommendations and we have no additional recommendations at this time.

[a]Abraham, S. Label and Labeling Review for Sincalide for Injection (NDA 210850). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2022 Nov 16. TTT ID No.: 2022-2110-1

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 16, 2022
Requesting Office or Division:	Division of Gastroenterology
Application Type and Number:	NDA 210850
Product Name and Strength:	Sincalide for Injection 5 mcg/vial
Submission date:	November 14, 2022
Applicant/Sponsor Name:	MAIA Pharmaceuticals Inc. (MAIA)
TTT ID#	2022-2110-1
DMEPA 1 Primary Reviewer:	Sherly Abraham, RPh
DMEPA 1 Team Leader:	Idalia Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 14, 2022 for Sincalide for Injection. Division of Gastroenterology (DG) requested that we review the revised label and labeling for Sincalide for Injection (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 revised is container label and carton labeling are unacceptable from a medication error perspective. Below, we have provided recommendations in Table 1 for the Applicant. We ask

[a]Abraham, S. Label and Labeling Review for Sincalide for Injection (NDA 210850). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2022 Nov 3. TTT ID No.: 2022-2110

that the Division convey Table 1 in its entirety to MAIA Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

Table 1. Identified Issues and Recommendations for MAIA Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton labeling and Container Label			
1.	As currently presented the dosage form (for injection) competes for prominence with the established name of the product.	Per our Guidance: Container and Carton, May 2022 (line 140-146, 188, 194-196) the proprietary name and established name of a drug product should be the most prominent information on the label and labeling.	Decrease the prominence of the dosage form on the label and labeling.
Carton Labeling			
1.	The back panel statement, (b) (4) (b) (4) is duplicated.	Duplicate statement on the back panel which is already present on the PDP may crowd the label and labeling and distract the reader from more important information on the back panel.	Delete the duplicate statement, (b) (4) (b) (4) from the back panel.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 3, 2022
Requesting Office or Division:	Division of Gastroenterology
Application Type and Number:	NDA 210850
Product Name and Strength:	Sincalide for Injection 5 mcg/vial
Submission date:	October 7, 2022
Applicant/Sponsor Name:	MAIA Pharmaceuticals Inc. (MAIA)
TTT ID#	2022-2110
DMEPA 1 Primary Reviewer:	Sherly Abraham, RPh
DMEPA 1 Team Leader:	Idalia Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), container label, and carton labeling received on October 7, 2022 for Sincalide for Injection. Division of Gastroenterology (DG) requested that we review the revised label and labeling for Sincalide for Injection (Appendix A) to determine if it is acceptable from a medication error perspective.

2 REGULATORY HISTORY

MAIA submitted a new NDA for Sincalide for Injection on August 25, 2017. We completed our label and labeling review[a] on January 16, 2018 and follow-up label and labeling memo[b] on February 16, 2018. On October 16, 2017, MAIA stated via email to OSE Project Manager that they intend to market this product under its generic name, Sincalide for Injection, and are not seeking a proprietary name at that time.[c]

The application received a tentative approval letter on February 23, 2018. MAIA resubmitted their application on September 26, 2022 for final approval. On November 2, 2022, MAIA stated again that they intend to market their product under its generic name, Sincalide for Injection, and are not seeking a proprietary name at this time.[d]

On October 7, 2022, MAIA stated that there are no proposed changes to PI, container label, and carton labeling.

3 CONCLUSION

Our evaluation of the proposed Sincalide for Injection PI found it acceptable; however, review of the submitted label and labeling identified areas of vulnerability in the container and carton label and labeling that may lead to medication errors. Below, we have provided recommendations in Table 1 for the Applicant. We ask that the Division convey Table 1 in its entirety to MAIA Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

Table 1. Identified Issues and Recommendations for MAIA Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton labeling and Container Label			

[a] Abraham, S. Label and Labeling Review for Sincalide for Injection (NDA 210850). Silver Spring (MD): FDA, CDER, OSE, DMEPA; 2018 JAN 16. RCM No.: 2017-1771

[b]Abraham, S. Label and Labeling Review Memo for Sincalide for Injection(NDA 210850). Silver Spring (MD): FDA, CDER, OSE, DMEPA; 2018 FEB 16. RCM No.: 2017-1771-1

[c]MAIA Pharmaceuticals USA, Inc. Email from Srikanth Sundaram(MAIA) to OSE Project Manager Shawnetta Jackson. Sincalide for Injection (NDA 210850). 2017 OCT 16.

[d] MAIA Pharmaceuticals USA, Inc. MAIA's Response to FDA's Proprietary Name Information Request. Sincalide for Injection (NDA 210850). 2022 NOV 2.
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80694b74&showAsPdf=true

Table 1. Identified Issues and Recommendations for MAIA Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	As currently presented, the established name, dosage form, and strength presentation have equal prominence.	Proprietary name and established name should be the most prominent information on the label per 21 CFR 201.10(g)(2).	Revise the presentations of the established name, dosage form, and strength in accordance with 21 CFR 201.10(g)(2). Take into account all pertinent factors, including typography, layout, contrast, and other printing features.
2.	The lot number statement is missing.	The lot number statement is required as per 21 CFR 201.10(i)(1).	Display the intended placement of the lot number statement.
3.	The expiration date is missing.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Display the intended placement of the expiration date and identify the format as recommended below: FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	The usual Dosage statement terminology is inconsistent with that used in the Prescribing Information.	21 CFR 201.55	To ensure consistency with the Prescribing Information, revise the statement (b) (4) (b) (4) to read "Recommended Dosage: See Prescribing Information."

Table 1. Identified Issues and Recommendations for MAIA Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	The route of administration (ROA) statement is incomplete.	Incomplete ROA statement can cause confusion to the healthcare providers.	Revise the ROA statement to read, "For intravenous use" similar to the carton labeling.
2.	As currently presented, the dosage form statement ("for injection") is split into two lines.	For NDAs, the dosage form statement should be located either on the same line as the active ingredient (established name) or directly below. USP General Chapter <7> Labeling USP General Chapter <1121>	Revise the dosage form presentation to be on one line.
3.	The Rx only statement and part of the NDC number are bolded.	Overuse of bold font may diminish its effect on prominence for other important product information.	Reserve the use of bolded font only for the most important product information on the label and labeling; remove bold font from the Rx only statement and NDC number.
4.	The storage information statement is missing the excursion information and referring to the PI as (b) (4) for the missing information.	Inconsistencies between PI and label and labeling may lead to misinterpretation in storage information.	Revise the storage statement to include accurate storage info and excursion information consistent to the PI. Delete the (b) (4) statement at the end of the storage statement.
5.	The side panel statements, "Single-Dose Vial. Discard Unused Portion, Store at 25C (77F)", are bolded.	Overuse of bold font may diminish its effect on prominence for important product information.	Reserve the use of bolded font only for the most important product information on the label and labeling; remove bold font on all other text.

Table 1. Identified Issues and Recommendations for MAIA Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
6.	The Rx only statement is found on the Principal Display Panel.	Per 21 CFR 201.10(i), the small label such as a vial label is required to have the following minimum amount of information: proprietary name, established name, product strength, Identifying lot or control number, name of manufacturer, packer, or distributor, and expiration date. Therefore, the Rx only statement is not required to be on the small vial label.	Delete or relocate the Rx only statement off the PDP.
7.	It is unclear if the linear barcode on the container label is scannable when placed around the curvature of the vial.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature.	Verify that the linear barcode on the container label is scannable when placed around the curvature of the vial.
Carton Labeling			
1.	It is unclear where the machine-readable product identifier and human-readable identifier are located on the label.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the machine-readable data matrix barcode to the carton labeling. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC]

Table 1. Identified Issues and Recommendations for MAIA Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date] We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.
2.	Part of the NDC number statement is bolded.	Overuse of bold font may diminish its effect on prominence for other important product information.	Reserve the use of bolded font only for the most important product information on the label and labeling; remove bold font from the NDC number.
3.	Post-dilution storage information to use the product within one hour is missing from the carton labeling.	Post-dilution storage information will inform patients preparing the product and minimize the risk of administering expired products.	Add post-dilution information to use the product within one hour to the back panel of carton labeling.
4.	Utilizing all black font on the PDP on a white background decreases the prominence of important product information.	Lack of prominence of important information on the PDP may lead to medication errors.	Consider using a different color font for the most prominent information such as established name and dosage form. Consider boxing the route of administration statement.
5.	The usage of symbols, (-), are noted in the storage statement.	The usage of symbols may cause	Replace the symbols with their intended meaning.

Table 1. Identified Issues and Recommendations for MAIA Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		misinterpretation and confusion.[e]	
6.	The back panel statements, (b) (4) (b) (4) (b) (4) are duplicated.	Duplicate information and statement on the back panel which are already present on the PDP may crowd the label and labeling and distract the reader from more important information on the back panel.	Delete the duplicate statements from the back panel.

[e]ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Appendix A: Label and Labeling Submitted on October 7, 2022

Container label:

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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 Surveillance and Epidemiology

Pharmacovigilance Review

Date:	November 3, 2022
Reviewer:	Michelle Hines, PharmD, BCPS Division of Pharmacovigilance I (DPV-I)
Team Leader:	Lisa Wolf, PharmD, BCPS DPV-I
Deputy Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Names:	Sincalide for Injection, Kinevac (sincalide)
Subject:	All adverse events
Application Type/Number:	NDA 210850 (Sincalide for Injection), NDA 017697 (Kinevac)
Sponsors:	MAIA Pharmaceuticals, Inc. (NDA 210850), Bracco Diagnostics Inc. (NDA 017697)
TTT Record ID:	2022-2469

1 INTRODUCTION

This review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), evaluates the FDA Adverse Event Reporting System (FAERS) database for all adverse events with Kinevac (sincalide) from March 26, 2016, to October 23, 2022. This memorandum will inform DG's review of New Drug Application (NDA) 210850, an original 505(b)(2) NDA with Kinevac (NDA 017697) as the reference-listed drug (RLD).

1.1 BACKGROUND

Sincalide is a cholecystopancreatic-gastrointestinal hormone peptide for parenteral administration that, when intravenously injected, stimulates gallbladder contraction and reduction in gallbladder size.[1]

On August 25, 2017, the Applicant submitted NDA 210850, for Sincalide for Injection, 5 mcg/vial, a 505(b)(2) application with Kinevac (NDA 017697, which was originally approved on July 21, 1976) as the RLD. NDA 210850 provides for the use of Sincalide for Injection in adults to:

- Stimulate gallbladder contraction, as may be assessed by various methods of diagnostic imaging, or to obtain by duodenal aspiration a sample of concentrated bile for analysis of cholesterol, bile salts, phospholipids, and crystals

- Stimulate pancreatic secretion in combination with secretin prior to obtaining a duodenal aspirate for analysis of enzyme activity, composition, and cytology

- Accelerate the transit of a barium meal through the small bowel, thereby decreasing the time and extent of radiation associated with fluoroscopy and x-ray examination of the intestinal tract

On February 23, 2018, FDA granted tentative approval for NDA 210850; at that time, the Applicant notified FDA that the patent owner for approved application holder for the RLD had initiated a patent infringement suit against the Applicant with respect to patent 6,803,046. Therefore, FDA did not grant final approval for NDA 210850 at that time and provided the Applicant with criteria for obtaining final approval for the application.

On August 16, 2022, the patent for RLD NDA 017697 Kinevac expired.

On September 23, 2022, the Applicant requested final approval of NDA 210850; furthermore, the Applicant requested an expedited review of the application because the RLD is in shortage. The Applicant provided a Safety Update Report,[2] which included an analysis of the FAERS Public Dashboard for reports with sincalide as the suspect drug from 2018 through 2022.

On October 24, 2022, DG consulted DPV-I to confirm the applicant's findings that there are no new reports in the FAERS database that constitute a new safety signal for the RLD.

1.2 PRIOR OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY REVIEW OF POSTMARKETING SAFETY OF SINCALIDE

On May 18, 2016, the Office of Surveillance and Epidemiology (OSE) completed a review of the postmarketing safety of sincalide, which included review of 119 reports submitted to the FAERS database from July 21, 1976, to March 25, 2016, and identified reports describing the unlabeled adverse events of anaphylaxis (n=12), seizure (n=8), and hypersensitivity reactions (n=6). Of note, of the eight cases of seizure, none provided detailed clinical information necessary for thorough assessment for a causal association with drug administration (e.g., past medical history, diagnostic testing, investigation of alternate causes), and five seizures occurred in the setting of anaphylaxis following sincalide administration. Furthermore, the review described cases of vasovagal reactions (n=6) associated with sincalide administration; at that time, the sincalide labeling discussed sincalide-induced vagal stimulation only in the OVERDOSAGE section.

The proposed labeling for Sincalide for Injection[1] describes anaphylaxis, anaphylactic shock, and other hypersensitivity reactions in WARNINGS AND PRECAUTIONS (5.1) and both seizure and vasovagal reactions in ADVERSE REACTIONS.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database for all adverse events with sincalide using the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*

Date of search	October 24, 2022
Time period of search	March 26, 2016,† to October 23, 2022
Search type	RxLogix PV Reports Profile Report
Product term	Product Active Ingredient: sincalide
MedDRA search terms (Version 25.1)	All events and all outcomes

* See **Appendix A** for a description of the FAERS database.
† Data-lock date of 2016 OSE review of all adverse events with sincalide

2.2 CAUSALITY ASSESSMENT

DPV-I assessed cases of any adverse event for a causal relationship with sincalide using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system as shown below in **Table 2**.

Table 2. Causality Classification and Criteria Based on the WHO-UMC System	
Causality Term	**Assessment Criteria**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon • Rechallenge satisfactory, if necessary
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

2.3 COMPARISON OF REPORTED ADVERSE EVENTS TO PROPOSED LABELING FOR SINCALIDE

The DPV-I reviewer conducted hands-on review of every report from the FAERS database search described in **Table 1** and compared the event(s) described to the proposed labeling for sincalide[1] to determine whether the report described labeled or unlabeled events.

3 RESULTS

3.1 FAERS DATA SUMMARY

The FAERS database search described in **Table 1** retrieved 57 reports. DPV-I performed hands-on review of all reports, which are summarized in **Table 3** below.

Table 3. Summary of Reports With Sincalide Reported to the FAERS Database From March 26, 2016, to October 23, 2022 (N=57)

Report Classification*	Reviewer's Comment
Drug ineffective (n=37†)	-All 37 reports of drug ineffectiveness stated that manufacturer quality assurance investigations identified no cause. -Of the 37 reports of drug ineffectiveness, 2 also reported the labeled adverse event of abdominal pain.
Labeled adverse event (n=9)	-Four reports described labeled hypersensitivity reactions, including one report of anaphylactic reaction (treatments/outcome unknown). -Two reports described events listed under vasovagal reactions within ADVERSE REACTIONS. -Two reports described abdominal pain. -One report described diarrhea and abdominal discomfort.
No adverse event (n=6)	-FAERS report 20120362 describes inconsistent and unclear expiration date labeling for sincalide packaging; DPV-I provided this report to the Division of Medication Error Prevention and Analysis (DMEPA) reviewer, who will provide a recommendation to the Applicant to ensure that the expiration date is in the correct format. -FAERS report 12376411 was submitted by a pharmacist and asserts that Kinevac reconstitution instructions are not consistent with USP 797; DG and the Office of Pharmaceutical Quality (OPQ) reviewer discussed this issue during FDA's prior review of NDA 210850 and concluded that USP 797 does not apply. -FAERS report 16706687 describes sincalide administration to a woman who underwent a hepatobiliary iminodiacetic acid (HIDA) scan with technicium/mebrofenin and sincalide because of abdominal pain who did not know that she was 4 weeks pregnant. The woman experienced no adverse events during the scan; no additional information about her pregnancy course or outcome is provided.
Unlabeled event (n=5)	-Five non-serious cases described unlabeled events with a possible causal association to sincalide administration (see **Appendix B** for line listing). - Three FAERS cases (i.e., 13912843, 13912844, 18397217) describe **injection-site reactions**; these cases are described in more detail in **Section 3.2**. Furthermore, we searched the FAERS database for any additional cases of injection-site reactions with sincalide through March 25, 2016, and found no other cases. -FAERS case 14586409 describes a patient (age/gender not reported) who was administered an unknown dose of sincalide; 2 hours later, the patient experienced **reddened palms**, which subsided 25 minutes later. The patient also received concomitant Choletec (Kit for Preparation of Technetium Tc 99m Mebrofenin) at an unspecified time relative to the event. The case did not specify whether the patient received treatment for the event. -FAERS case 12691096 describes a 33-year-old woman who was administered sincalide for a HIDA scan to evaluate for possible biliary tract disease. The scan was completed without incident and later that same day, the patient reported onset of **myalgia** and **flu-like symptoms**. No treatment was administered and the events resolved spontaneously on an unknown date.

Table 3. Summary of Reports With Sincalide Reported to the FAERS Database From March 26, 2016, to October 23, 2022 (N=57)	
Report Classification*	**Reviewer's Comment**
Unassessable (n=2)	-Two reports had limited information to assess the event or causal relationship to sincalide.

* Report classifications were determined by the DPV-I reviewer.

Reviewer's comment: It is possible that reddened palms was a mild hypersensitivity reaction, and the proposed labeling for sincalide describes hypersensitivity reactions; furthermore, it is unclear whether the event can also be attributed to Choletec administration. Therefore, we do not propose describing reddened palms in the labeling for sincalide based on this case. The events myalgia and flu-like symptoms had a possible causal relationship to sincalide administration; these cases were non-serious and resolved without treatment. We do not propose including myalgia or flu-like symptoms in the labeling for sincalide based on this single case.

3.2 SUMMARY OF INJECTION-SITE REACTIONS WITH SINCALIDE ADMINISTRATION

Three nonserious cases of unlabeled injection-site reactions following sincalide administration, including injection-site swelling (n=3), pain (n=1), or redness (n=1), are described below. All three cases had a possible causal relationship to sincalide administration. Of the three cases, one was treated with a warm compress, one did not require treatment, and one did not report information about treatment.

- **FAERS case 13912843, United States, non-serious, Periodic report, 2017:** A 67-year-old woman underwent a "contrast-enhanced" HIDA scan for an unknown reason with intravenous (IV) sincalide injection. On the same day, after an unknown interval of time following sincalide administration, she experienced **injection site redness and swelling**, which subsided without treatment on the same day.

- **FAERS case 13912844, United States, non-serious, Periodic report, 2017:** A woman (age not reported) underwent a "contrast-enhanced" HIDA scan with IV sincalide injection into the right hand to evaluate gallbladder function. "After" sincalide administration, the patient experienced "extravasation with symptoms of arm **pain and swelling** from hand to wrist"; the patient did not experience arm redness. The patient applied warm compress to her right hand for treatment and at the time of reporting the events were resolving.
  *Reviewer's comment: Sincalide is not a known vesicant drug; the reporter used the word "*extravasation*," but is likely describing IV-line infiltration.*

- **FAERS case 18397217, United States, non-serious, Direct report, 2020:** An 87-year-old man was administered IV sincalide into the right lower arm for a HIDA scan. Prior to infusion, the IV line flushed well; the patient did not complain of pain or discomfort during the infusion. After the infusion was complete, the nurse noticed **IV site swelling**. Information about the outcome or treatment for the event was not reported.

4 DISCUSSION

DPV-I performed hands-on review of all 57 reports with sincalide reported to the FAERS database from March 26, 2016, to October 23, 2022. Among the 57 reports, most (n=37) described drug ineffectiveness, 9 described events that are included in the proposed labeling for sincalide, 6 did not describe an adverse event, 5 described unlabeled events, and 2 were unassessable. None of the nine reports of labeled adverse events described an increased severity for the event compared to the proposed sincalide labeling. Furthermore, we did not identify any new cases of seizure, which was a potential safety signal from the 2016 OSE review.

All five cases of unlabeled adverse events were nonserious and had a possible causal relationship to sincalide. Three of the five cases described injection-site reactions, including injection site swelling (n=3), pain (n=1), or redness (n=1). Of the three injection-site reactions, one was treated with a warm compress, and the remaining two did not require treatment (n=1) or did not report information about treatment (n=1). Of the five cases of unlabeled adverse events, the remaining two cases included reddened palms, which may represent a mild hypersensitivity reaction, and myalgia/flu-like symptoms; the events described in both cases resolved without treatment.

Because of the low number and mild severity among all five cases of unlabeled adverse events, DPV-I does not recommend adding any new terms to the sincalide labeling.

5 REFERENCES

1. Sincalide for injection [package insert]. Princeton, NJ: MAIA Pharmaceuticals, Inc. Proposed labeling revised February 2018. Available at \\CDSESUB1\EVSPROD\nda210850\0014\m1\us\12-cover-letters\tentative-approval-letter.pdf

2. Safety Update Report for Sincalide for Injection, 5 mcg/vial. New Drug Application 210850, MAIA Pharmaceuticals, Inc. Available at \\CDSESUB1\EVSPROD\nda210850\0014\m5\53-clin-stud-rep\535-rep-effic-safety-stud\stimulate-gallbladder-contraction\5353-rep-analys-data-more-one-stud\iss\safety-update-report.pdf

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.2 APPENDIX B. LINE LISTING OF CASES OF UNLABELED ADVERSE EVENTS WITH SINCALIDE REPORTED TO THE FAERS DATABASE FROM MARCH 26, 2016, TO OCTOBER 23, 2022

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Report Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	26-AUG-2016	12691096	1	US-BRACCO-012381	Periodic	33	Female	United States	
2	28-AUG-2017	13912843	1	US-BRACCO-014783	Periodic	67	Female	United States	
3	28-AUG-2017	13912844	1	US-BRACCO-014511	Periodic		Female	United States	
4	01-MAR-2018	14586409	2	US-BRACCO DIAGNOSTICS, INC.-2017US04435	Periodic			United States	
5	16-OCT-2020	18397217	1	FDA-CDER-CTU-2020-89911	Direct	87	Male	United States	

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those that are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.

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/s/

MICHELLE C HINES
11/03/2022 03:48:54 PM

LISA M WOLF
11/03/2022 04:02:51 PM

MONICA MUNOZ
11/03/2022 04:07:05 PM

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:	February 16, 2018
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 210850
Product Name and Strength:	Sincalide for Injection 5 mcg/vial
Submission date:	February 12, 2018
Applicant/Sponsor Name:	Maia Pharmaceuticals Inc.
OSE RCM #:	2017-1771-1
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised carton labeling, container label (Appendix A) and prescribing information (PI) 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, OSE RCM #: 2017-1771[a].

2 CONCLUSION

We find the revised carton labeling, container label and PI acceptable from a medication error perspective and have no further recommendations at this time.

[a]Abraham.S. Label and Labeling Review for sincalide (NDA210850). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2018 01 16. 32 p. OSE RCM No.:2017-1771

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/s/

SHERLY ABRAHAM
02/16/2018

SARAH K VEE
02/16/2018

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

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

Memorandum

Date: January 24, 2018

To: Benjamin Vali, Regulatory Project Manager, DGIEP

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for SINCALIDE FOR INJECTION

NDA: 210850

In response to DGIEP's consult request dated 11/7/17, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for SINCALIDE FOR INJECTION.

PI: OPDP has no comments on the proposed labeling based on the draft PI retrieved from SharePoint on January 24, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor, retrieved from SharePoint on January 24, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
01/24/2018

Medical Officer's Consultative Review Memorandum

Submission:	NDA 210850
Sponsor:	MAIA Pharmaceuticals, Inc.
Product:	Cholecystokinin
Proposed Indication:	Sincalide for Injection is a cholecystokinetic drug indicated: (1) to stimulate gallbladder contraction, as may be assessed by various methods of diagnostic imaging, or to obtain by duodenal aspiration a sample of concentrated bile for analysis of cholesterol, bile salts, phospholipids, and crystals; (2) to stimulate pancreatic secretion (especially in conjunction with secretin) prior to obtaining a duodenal aspirate for analysis of enzyme activity, composition, and cytology; (3) to accelerate the transit of a barium meal through the small bowel, thereby decreasing the time and extent of radiation associated with fluoroscopy and x-ray examination of the intestinal tract**.**
Requested by:	Benjamin Vali, DGIEP, CDER
Consulting Reviewer:	Brenda Ye, M.D., Division of Medical Imaging Products
Through:	Nushin Todd, M.D., Ph.D., Team Leader, DMIP Alex Gorovets, M.D., Deputy Director, DMIP
Consult Request Date:	January 7, 2018
Consult Completion Date:	January 24, 2018

Consulting Division's Questions:

DGIEP received a 505(b)(2) NDA on August 25, 2017 (eCTD SN0000) for 'Sincalide for Injection', which (for eventual approval) will rely on FDA's findings of safety and/or effectiveness for reference listed drug (RLD) KINEVAC (NDA 017697).

In response to an FDA information request, the sponsor subsequently submitted their Pregnancy and Lactation Labeling Rule (PLLR) compliant prescribing information (PI) on October 20, 2017 (eCTD SN0001). This submission signified the sponsor's proposed PI. Due to current KINEVAC drug shortages, this new NDA was granted priority review designation, which resulted in a PDUFA Goal Date of February 25, 2018 (Action Goal Date: February 23, 2018).

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/s/

BRENDA Q YE
01/24/2018

ALEXANDER GOROVETS
01/24/2018

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

Division of Pediatric and Maternal Health Review

Date: 1/12/2018 **Date consulted:** 11/7/2017

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

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

To: Division of Gastrointestinal and Inborn Errors Products (DGIEP)

Drug: Sincalide for Injection

NDA: 210850

Applicant: MAIA Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: - to stimulate gallbladder contraction, as may be assessed by various methods of diagnostic imaging, or to obtain by duodenal aspiration a sample of concentrated bile for analysis of cholesterol, bile salts, phospholipids, and crystals;
- to stimulate pancreatic secretion prior to obtaining a duodenal aspirate for analysis of enzymatic activity, composition, and cytology;
- to accelerate the transit of a barium meal through the small bowel, thereby decreasing the time and extent of radiation associated with fluoroscopy and x-ray examination of the intestinal tract.

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 210850

- DPMH consult request dated 11/7/2017, DARRTS reference ID 4177988

Consult Question: "DGIEP kindly requests assistance from the Maternal Health Team of DPMH in the evaluation of Section 8 of the PI, specifically whether the sponsor correctly presented this section to be consistent with the PLLR. A review of all submitted literature to support the PLLR is also requested."

INTRODUCTION

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on November 11, 2017, requesting input regarding the applicant's labeling proposal, specifically the proposed Pregnancy and Lactation (PLLR) language (subsections 8.1/8.2).

REGULATORY HISTORY

- On August 25, 2017, the applicant, MAIA, submitted a new 505(b) (2) NDA for Sincalide for Injection, 5mcg/vial based on the listed drug relied upon (listed drug), KINEVAC (sincalide) for Injection, NDA 017697. KINEVAC (sincalide) for Injection was originally approved for use in the U.S. market on July 21, 1976.
- The applicant was granted a priority review of NDA 210850 because the relied-upon listed drug, KINEVAC (sincalide) for Injection, is currently in shortage and has been listed in the American Society of Health-System Pharmacists (ASHP) Drug Shortages Database since March 1, 2017. There are no approved alternatives to KINEVAC for the labeled indications.

BACKGROUND

Drug Characteristics[1]

- Sincalide is a cholecystopancreatic-gastrointestinal hormone. It is a synthetically prepared C-terminal octapeptide of cholecystokinin (CCK).
- When injected intravenously, sincalide causes the gallbladder to contract and stimulates pancreatic secretion and intestinal motility.
- The molecular weight is 1143.27 Daltons.
- The serum half-life of sincalide is (b) (4)
- Bioavailability and protein binding were not described.
- Sincalide is contraindicated in patients with hypersensitivity to sincalide and in patients with intestinal obstruction.
- Known adverse reactions include abdominal pain and cramping and nausea.

Gall Bladder Disease and Pregnancy

- The reported incidence of gallstone-related disease in pregnant women is 0.05-0.33%.[2,3,4]

[1] Sincalide for injection (sincalide) Proposed Package Insert
[2] Ellington SR, et al. Recent trends in hepatic diseases during pregnancy in the United States, 2002-2010. Am J Obstet Gynecol. 2015;212(4):524.e1.
[3] Date RS, et al. A review of the management of gallstone disease and its complications in pregnancy. Am J Surg. 2008;196(4):599.

- According to the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), laparoscopic cholecystectomy is the treatment of choice in pregnant patients with symptomatic gallbladder disease, regardless of trimester.[5]
- Recurrent gallbladder symptoms develop in 92% of patients managed non-operatively in the first trimester, in 64% of patients who presented in the second trimester and in 44% of patients who present in the third trimester.[6,7]
- Approximately 50% of patients with recurrent symptoms require hospitalization and may experience preterm labor in 20% of cases and fetal loss in 10-60% of cases.[8,9]

Current State of the Labeling for KINEVAC (sincalide) for Injection[10]

- The current labeling for the relied-upon listed drug, KINEVAC (sincalide) for Injection, is not in Physician Labeling Rule (PLR) format.
- There is no boxed warning for embryofetotoxicity.
- There is a warning for a risk of spontaneous abortion or preterm labor if used during pregnancy (based on mechanism of action –smooth muscle relaxation).
- No clinical or non-clinical data are presented in the Pregnancy or Nursing Mothers subsections of the labeling.
- There are no existing pregnancy testing/contraception recommendations.
- There are no known drug-drug interactions with hormonal contraceptives.

REVIEW
PREGNANCY

Nonclinical Experience

In a prenatal development study in which pregnant rats were administered sincalide during organogenesis through parturition, decreased weight gain and developmental delays were administered were observed at a dose 122-times the maximum recommended human dose on a mg/kg basis.[11] The reader is referred to the full Pharmacology/Toxicology review by Tamal Chakraborti, Ph.D. and Sushanta Chakder, Ph.D.

Applicant's Review of Literature

The applicant reported performing a search of PubMed using key words, "sincalide," or "KINEVAC." No studies of the effects of sincalide in pregnant humans were identified in the

[4] Elamin Ali M, et al. Is surgical intervention in acute cholecystitis in pregnancy justified? J Obstet Gynecol. 1997;17(5):435-8.
[5] Pearl JP, et al. Guidelines for the use of laparoscopy during pregnancy. Society of American Gastrointestinal and Endoscopic Surgeons Guidelines. May, 2017. https://www.sages.org/publications/guidelines/guidelines-for-diagnosis-treatment-and-use-of-laparoscopy-for-surgical-problems-during-pregnancy/ accessed. 12/26/2017.
[6] Steinbrook RA, et al. Laparoscopic cholecystectomy during pregnancy. Review of anesthetic management, surgical considerations. Surg Endosc. 1996;10:551-515.
[7] Date RS, et al. A review of the management of gallstone disease and its complications in pregnancy. Am J Surg. 2008;196:599-608.
[8] Scott LD. Gallstone disease and pancreatitis in pregnancy. Gastroenterol Clin North Am. 1992;21:803-815.
[9] Othman MO, et al. Conservative management of cholelithiasis and its complications in pregnancy is associated with recurrent symptoms and more emergency department visits. Gastrointest. Endosc. 2012;76:564-569.
[10] Kinevac (sincalide) for Injection, Daily Med, accessed 12/11/2017.
[11] Sincalide for injection NDA 210850, PLLR review. MAIA Pharmaceuticals, Inc.

PLLR review document, but in the applicant's Integrated Summary of Safety, a case report describing a case of threatened abortion is reported[12] (see DPMH Review of Literature for details).

DPMH Review of Literature

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex[13] using the search terms, "sincalide and pregnancy," "sincalide and pregnant women," "sincalide and pregnancy and birth defects," "sincalide and fetal malformations," "sincalide and stillbirth," and "sincalide and miscarriage."

Reprotox[14] states, "Sincalide did not produce anomalies in rat fetuses at doses up to 12.5 times the maximum human dose."

A search of the published literature yielded one case report describing a case of a woman who was six weeks pregnant and experienced vaginal bleeding and uterine contractions within 5 minutes of the injection of sincalide. An ultrasound was obtained which showed the presence of a yolk sac. The final diagnosis was threatened abortion. No additional detail or follow-up information was provided.[15] This case was reported to FDA and resulted in a change in the labeling with the addition of the following language in the Warnings section: "Because of KINEVAC's effect on smooth muscle, pregnant patients should be advised that spontaneous abortion or premature induction of labor may occur."

Review of Pharmacovigilance Database

The applicant described a review of the FDA Adverse Event Reporting System (FAERS) from January 1976 through December 2013. The applicant reports no cases related to pregnancy, other than the previously mentioned case of threatened abortion.

Summary

Human data on the effect of sincalide on the developing fetus are not available. Animal data report an impact on fetal weight gain and development with sincalide administration in pregnant rats, but at doses 122 times the maximum recommended human dose. Current labeling in the WARNINGS section contains language to inform pregnant women of the risk of spontaneous abortion or preterm labor based on mechanism of action (smooth muscle relaxation). There is one case report in the literature of threatened spontaneous abortion. DPMH recommends keeping the warning related to spontaneous abortion and preterm labor.

LACTATION

Nonclinical Experience

There are no data available from animal studies on the excretion of sincalide into milk.

Applicant's Review of Literature

The applicant performed a literature search; search parameters were not provided.

[12] Silberstein EB, Marcus CS. Unreported side effect of sincalide. Radiology. 1994;190:902.
[13] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 12/26/2017
[14] 2017 Reproductive Toxicology Center. Accessed 12/26/2017.
[15] Silberstein EB, Marcus CS. Unreported side effect of sincalide. Radiology. 1994;190:902.

The applicant reported two papers related to lactation.

- A lactation study of twenty-eight women who delivered healthy infants at term had CCK measured 3 hours after the first morning nursing period on postpartum days 3,4, and 5 and postpartum weeks 1, 2, 4, 6 and months 3-6. CCK was approximately half of the normal plasma concentration in the first postpartum week, and decreased by 50% by the second postpartum week and by 75% by 3 months postpartum.[16]
- Samples of breast milk were collected from ten mothers who had delivered term infants and ten mothers who delivered preterm infants. Ghrelin and CCK levels were measured using radioimmunoassay (RIA). CCK levels in breast milk samples were negligible and were not affected by infant gestational age, birthweight, maternal age, or maternal pre-pregnancy body mass index.[17]

DPMH Review of Literature

DPMH conducted a search of *Medications in Mother's Milk*[18], the Drugs and Lactation Database (LactMed),[19] Micromedex,[13] and of the published literature in PubMed and Embase using the search terms "sincalide and lactation," and "sincalide and breastfeeding."

Thomas Hale, a breastfeeding expert, rates sincalide as "L3- no data – probably compatible."[20]

Sincalide is referenced in LactMed[19] which states, "Sincalide is a synthetic octapeptide analogue of cholecystokinin. Because sincalide has a molecular weight of 1143, the amount in milk is likely to be very low and oral absorption by the infant is unlikely because it is probably destroyed in the infant's gastrointestinal tract. The serum half-life of sincalide is less than 2 minutes, indicating that withholding breastfeeding for 10 minutes after a dose should ensure that the infant is not exposed to the drug."

A search of the literature did not yield any additional reports.

Review of Pharmacovigilance Database

The applicant did not report on cases related to lactation.

Summary

[16] Berseth CL et al. Postpartum changes in pattern of gastrointestinal regulatory peptides in human milk. Am J Clin Nutr. 1990;51:985-90.
[17] Kierson JA, et al. Ghrelin and cholecystokinin in term and preterm human breast milk. Acta Paediatrica. 2006;95:991-995.
[18] Hale TW and Rowe HE. (2017) Medications and Mother's Milk. Springer Publishing Company, LLC. New York, NY.
[19] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal 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.
[20] Hale TW and Rowe HE. (2017) Medications and Mother's Milk. Springer Publishing Company, LLC. New York, NY. pp.873-4.

Cholecystokinin is present in breast milk in low levels; no data are available specific to sincalide in human lactation. The high molecular weight (>800 Daltons), poor oral bioavailability, and short half-life (2.5 to 3 minutes) of sincalide make it less likely that sincalide will pass into breastmilk and accumulate. DPMH recommends the following language be added to labeling.

> "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sincalide for injection and any potential adverse effect on the breastfed infant from Sincalide for injection or from the underlying maternal condition."

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No studies of the effect of sincalide on fertility were reported. The applicant described a paper that reported no adverse effect of CCK on mating behavior in male and female rats. [21]

Applicant's Review of Literature

The applicant performed a literature search; search parameters were not provided.

No studies specific to the effects of sincalide on human fertility were reported.

DPMH Review of Literature

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "sincalide and fertility," "sincalide and contraception," "sincalide and oral contraceptives," and "sincalide and infertility."

No papers on the effects of sincalide and either fertility or hormonal contraception were located.

Review of Pharmacovigilance Database

No cases related to fertility and sincalide were reported.

Summary

No data are available on the effects of sincalide on human fertility or hormonal contraception. Limited data with animals do not indicate an adverse effect of sincalide on fertility. Subsection 8.3 will not be included in labeling.

CONCLUSIONS

The Pregnancy and Lactation subsections of Sincalide for Injection labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Subsection 8.1**
  - The "Pregnancy" subsection of labeling was formatted in the PLLR format to include: "Risk Summary" and "Data" subheadings.
- **Lactation, Subsection 8.2**

[21] Kaplan JM, et al. Simultaneous display of sexual and ingestive behavior by rats. J Neuroendocrinol. 1992;4:381-392.

- The "Lactation" subsection of labeling was formatted in the PLLR format to include: the "Risk Summary" subheading.
- **Patient Counseling Information, Section 17**

The "Patient Counseling Information" subsection of labeling was updated to correspond with changes made to subsections 8.1 and 8.2 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 5.3, 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

- Advise pregnant women of the potential risk for preterm labor or spontaneous abortion due to the effect of sincalide on smooth muscle. (5.3, 8.1)

FULL PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

5.3 Preterm Labor or Spontaneous Abortion

Based on limited human data and mechanism of action, advise pregnant patients that Sincalide for Injection may cause preterm labor or spontaneous abortion *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on limited human data and mechanism of action, Sincalide for Injection may cause preterm labor or spontaneous abortion *[see Warnings and Precautions (5.3)]*. Limited available data with Sincalide for Injection are insufficient to inform a drug-associated risk of adverse developmental outcomes. In animal embryo-fetal development studies in which sincalide was administered to hamsters and rats during the period of organogenesis, no effects were seen at doses comparable to the maximum recommended human dose on a mg/kg basis. However, in a prenatal development study in which rats were administered sincalide during organogenesis through parturition, decreased weight gain and developmental delays were observed at a dose 122 times higher than the maximum recommended human dose based on body surface area.

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

Data

Animal Data

There were no effects on embryo-fetal development in hamsters when sincalide was administered subcutaneously at 250 or 750 ng/kg during organogenesis (Gestation Days 7 to13) at doses up to 0.8 times the maximum recommended dose of 120 ng/kg on a body surface area basis. No effects on embryo-fetal development were observed in Sprague-Dawley rats at subcutaneous doses of 250, 450, or 750 ng/kg from Gestation Days 6 to 16, representing 1.0 time the maximum recommended human dose on a body surface area basis. In a separate study at a higher dose of 90 mcg/kg administered subcutaneously to CFY rats from Gestation Day 10 through parturition (representing 122 times the maximum recommended human dose on a body surface area basis), offspring showed decreased growth, behavioral changes, and developmental delays.

8.2 Lactation

Risk Summary

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

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise pregnant women of the potential risk for preterm labor or spontaneous abortion. *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*

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/s/

CATHERINE A ROCA
01/12/2018

MIRIAM C DINATALE
01/12/2018

LYNNE P YAO
01/17/2018

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:	January 16, 2018
Requesting Office or Division:	Division of Gastrointestinal and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 210850
Product Name and Strength:	Sincalide for Injection 5 mcg/vial
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Maia Pharmaceuticals Inc.
Submission Date:	August 25, 2017 October 20, 2017
OSE RCM #:	2017-1771
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Sincalide for Injection (NDA 210850), 505 (b)(2) NDA, submitted on August 25, 2017. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information, container label, and carton labeling for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS 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

Maia Pharmaceuticals Inc.submitted a 505 (b) (2) NDA for Sincalide for Injection on August 25, 2017. The reference listed drug for this product is Kinevac (sincalide) for Injection, NDA 017697. We note that the proposed product has the same active ingredient, dosage form, strength, route of administration and indications as the reference listed product.

We identified areas in the Prescribing Information (PI), container label, and carton labeling that can be improved to increase the clarity of information to promote the safe use of the product. We defer to Office of Pharmaceutical Quality (OPQ) for the correct

usage of container term (single dose vs. single use). We communicated some changes and clarifications to the PI directly in the sharepoint document provided by DGIEP. We provide an additional recommendation for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed prescribing information, container labels, and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. We provide our recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATION FOR THE DIVISION

A. FULL PRESCRIBING INFORMATION: Section 2.2 Preparation and Administration

1. We note that the storage time for the post dilution intravenous infusion is very short. We recommend bolding the storage statements, "Store the (b) (4) diluted solution at room temperature (b) (4) one hour. Discard unused portion." We recommend this to increase the prominence of this important information and to inform persons responsible for preparing the product and minimize the risk of administering expired products.

4.2 RECOMMENDATIONS FOR MAIA PHARMACEUTICALS INC.

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

A. Carton Labeling:

1. Ensure that both lot number and expiration date are printed on all labels.[a]

B. Container Label Only:

2. We recommend that the strength statement be expressed in terms of the total amount of drug per vial (5 mcg/vial) similar to the carton labeling.[a]

[a] Draft Guidance for Industry: Safety Consideration for container labels and carton labeling design to minimize medication errors. 2013.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for sincalide that Maia Pharmaceuticals Inc.submitted by on August 25, 2017 and October 20, 2017.

Table 2. Relevant Product Information for Sincalide for Injection	
Initial Approval Date	July 21, 1976
Active Ingredient	sincalide
Indication	To stimulate gallbladder contraction, as may be assessed by various methods of diagnostic imaging, or to obtain by duodenal aspiration a sample of concentrated bile for analysis of cholesterol, bile salts, phospholipids, and crystals; To stimulate pancreatic secretion (especially in conjunction with secretin) prior to obtaining a duodenal aspirate for analysis of enzyme activity, composition, and cytology; To accelerate the transit of a barium meal through the small bowel, thereby decreasing the time and extent of radiation associated with fluoroscopy and x-ray examination of the intestinal tract.
Route of Administration	Intravenous or intramuscular
Dosage Form	Injection
Strength	5 mcg/vial
Dose and Frequency	To stimulate contraction of the gallbladder <u>Intravenous Injection</u> 0.02 mcg/kg as a single dose over 30 to 60 seconds. If satisfactory contraction does not occur in 15 minutes, administer a dose of 0.04 mcg/kg over 30 to 60 seconds. <u>Intravenous Infusion to Reduce Gastrointestinal Adverse Reactions</u> 0.12 mcg/kg diluted in 100 mL of 0.9% Sodium Chloride Injection USP and infused over 50 minutes (rate of 2 mL per minute).

	Intramuscular Injection 0.1 mcg/kg as a single dose To stimulate pancreatic secretion 30 minutes after secretin for injection Intravenous Infusion 0.02 mcg/kg diluted in 30 mL of 0.9% Sodium Chloride Injection USP and infused over 30 minutes at a rate of 1 mL/minute. To accelerate the transit of a barium meal through the small intestine: Intravenous Injection After the barium meal is beyond the proximal jejunum, administer 0.04 mcg/kg over 30 to 60 seconds. If satisfactory transit of the barium meal has not occurred in 30 minutes, administer a dose of 0.04 mcg/kg over 30 to 60 seconds. Intravenous Infusion to Reduce Gastrointestinal Adverse Reactions 0.12 mcg/kg diluted to approximately100 mL 0.9% Sodium Chloride Injection USP and infused over 30 minutes
How Supplied	Sincalide for Injection is supplied in packages of 10 vials containing 5 mcg of sincalide per vial
Storage	Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [See USP Controlled Room Temperature].
Reference Listed Drug	Kinevac (sincalide) for Injection NDA 017697

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,[b] along with postmarket medication error data, we reviewed the following sincalide labels and labeling submitted by Maia Pharmaceuticals Inc. on August 25, 2017 and October 20, 2017.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container label:

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

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

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/s/

SHERLY ABRAHAM
01/16/2018

SARAH K VEE
01/16/2018