CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210850Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	210850
Submission Date	August 25, 2017
SDN:	1
Brand Name:	Sincalide for Injection (5 mcg/vial)
Generic Name:	Sincalide
Proposed Indication:	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.
Reviewer:	Jie Cheng, Ph.D.
Team Leader:	Insook Kim, Ph.D.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	CDER/ODE3/Division of Gastroenterology and Inborn Errors Products
Sponsor:	MAIA Pharmaceuticals, Inc.
Submission Type:	Original NDA 505 (b)(2)
Review Priority:	Standard

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1. Executive Summary

This is an original NDA submission for "Sincalide for Injection", 5 mcg/vial, pursuant to Section 505(b)(2) by relying on the Agency's findings of efficacy and safety for KINEVAC(sincalide) (NDA 017697) for Injection. The proposed indication and the dosage regimen is the same as for KINEVAC. There are no clinical pharmacology studies conducted with the proposed product and the applicant requested a biowaiver for in vivo relative bioavailability study between KINEVAC and the proposed product.

The product is a sterile, pyrogen-free, lyophilized powder consisting of 5 mcg of active ingredient, sincalide, in single-use clear glass vials. When used, the powder will be reconstituted aseptically with 5 mL water for intravenous to the final concentration of 1 mcg/ml.

The sponsor did not conduct an in vivo bioequivalence study and requested a biowaiver for the relative BA/BE study between the listed drug and Sincalide for Injection. There is no clinical pharmacology related concern for granting a biowaiver as the final drug concentration prior to injection, and the dosing instruction are the same between KINEVAC and Sincalide for Injection. Refer to the biopharmaceutics review for the final decision on the biowaiver.

This review is focused on the clinical pharmacology related information in the proposed labeling for Sincalide solution in Sections 7-Drug Interaction, and 12.3-Pharmacokinetics.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed the submission, and found acceptable for approval from a clinical pharmacology perspective.

2. Review of the Submissions

The proposed indication and the dosage regimen is the same as for KINEVAC.

Proposed indication

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.

Dosage and Administration

The dosage and administration regimen varies for each indication (proposed dosing table (shown

as below) is pending approval which was recommended by the Agency in the labeling comments dated 2/1/2018 and accepted by the applicant in the IR response dated 2/9/2018):

Indication	**Sincalide for Injection Dosing and Administration Instructions**
To stimulate contraction of the gallbladder	0.02 mcg/kg as a single dose over 30 to 60 seconds via intravenous injection. If satisfactory contraction does not occur in 15 minutes, administer a dose of 0.04 mcg/kg over 30 to 60 seconds. Intravenous Infusion to Reduce Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.3)]* 0.12 mcg/kg diluted in 100 mL of 0.9% Sodium Chloride Injection USP and infused over 50 minutes at a rate of 2 mL per minute)
To stimulate pancreatic secretion 30 minutes after secretin for injection	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 per minute
To accelerate the transit of a barium meal through the small intestine	After the barium meal is beyond the proximal jejunum, administer 0.04 mcg/kg over 30 to 60 seconds via intravenous injection. If satisfactory transit of the barium meal has not occurred in 30 minutes, administer a second dose of 0.04 mcg/kg over 30 to 60 seconds. Intravenous Infusion to Reduce Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.3)]* 0.12 mcg/kg diluted in 100 mL 0.9% Sodium Chloride Injection USP and infused over 30 minutes

Formulation
Compared to the listed drug, KINEVAC for Injection (patent expired till August 16, 2022), the formulation for Sincalide for Injection is different for excipients, and pH shown as follows:

Listed Drug (KINEVAC (sincalide) for Injection, 5 mcg/vial)		MAIA Product (Sincalide for Injection, 5 mcg/vial)	
Ingredient	**Amount/vial**	**Ingredient**	**Amount**
Mannitol	170 mg	Mannitol USP	170 mg
Arginine hydrochloride	30 mg	Arginine hydrochloride USP	30 mg
Lysine hydrochloride	15 mg	Lysine hydrochloride USP	15 mg
Potassium phosphate dibasic	9 mg		
Methionine	4 mg	Methionine USP	4 mg
Pentetic acid	2 mg	Pentetic acid USP	2 mg
Sodium metabisulfite	0.04 mg	Sodium metabisulfite USP	0.04 mg
Polysorbate 20	0.005 mcg		
Sodium hydroxide/ Hydrochloric acid	Q.S to pH 6.0 to 8.0	Sodium hydroxide NF/ Hydrochloric acid NF	**Q.S to pH 6.5 to 7.5**

Recommended Revisions to the proposed label

Following recommendations on labeling were conveyed to the sponsor dated 2/1/2018. The revised labeling was received dated 2/9/2018 and is acceptable to the reviewer.

Since sincalide potentially interacts with other drugs and there is no DDI section (Section 7) in the original proposed labeling, the Agency conveyed the recommendations on DDI section along with recommendations on sincalide pharmacokinetic profile (Section 12.3) which was not included in the original proposed labeling. The labeling recommendations and sponsor response are as follows:

1. Reviewer's recommended update in Section 7. Drug Interaction

We recommend the sponsor to add the following paragraph:

> Drugs that relax the gallbladder including Opiate and anticholinergic drugs should be withheld for at least 48 hours before testing. Other drugs that may affect gallbladder contraction and that should not be taken within 24 hours prior to the study include nifedipine, indomethacin, octreotide, theophylline, benzodiazepines, phentolamine, isoproterenol, isoproterenol and progesterone. Nicotine and alcohol may also affect gallbladder contraction.
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> Reviewer's comment:
> The section 7 of "Drug interaction" was not originally included in the label for the listed drug. Nevertheless, the reviewer considers the recommendation is relevant based upon the mechanism of action of sincalide and published literature. Sincalide interacts with medications that affect gall bladder contraction (for example, but not limited to, opiates and anticholinergic drugs. Clinical Nuclear Medicine Issue: Volume 37(1), January 2012, p 63–70).
>
> The Agency also recommended the sponsor to provide additional categories of drugs as appropriate based on up-to-date literature, and provide the complete citations to us for our review. The time window between discontinuation of a concomitant medication and administration of sincalide may need to be adjusted based upon other categories of drugs.

Sponsor Response: We acknowledge that the wording proposed by FDA is based on the consensus recommendation of an interdisciplinary panel of experts (Dibaise JK et. al., 2012, Clin. Nucl. Med., 37, 63-70, 2012), and have therefore accepted it. We have not found any specific studies or literature that provide supportive data for the recommendations therein, specifically for the time windows stated.
Nevertheless, we believe it is appropriate to defer to current recommended medical practice.

Reviewer's comment: Without specific studies or literature documentation, other than treatment guidelines, we recommended not to include specific examples. The recommendation is further edited as follows:
"**7.1 Drugs that Affect Gallbaldder Motility or Contractile Response**
Drugs that may stimulate or inhibit gallbladder motility or contractile response, may interfere with the response to sincalide. Consider discontinuing these drugs prior to administration of Sincalide for Injection, when used to simulate contraction of the gallbladder."

2. Reviewer's recommended update in Section 12.3.
We recommended the sponsor to add the sentence "The serum half-life of sincalide is 2.5 to 3 minutes following intravenous injection."

Reviewer's comment: The section 12.3 was not contained in the proposed labeling originally. The recommendation was added based on the following references:

Hedner P, et al. Am J Roentgenol Radium Ther Nucl Med 1972 Oct:116(2):320-6.
Krishnamurthy GT, et al. Eur J Nucl Med Mol Imaging 2004 Jan;31(1):85-93.
Rosenquist CJ, et al. Radiology 1983 Jan:146(1):21-3.

Sponsor Response: We have accepted the Agency's proposed language. The half-life stated is likely based on the primary pharmacokinetic data in Thompson JC et al 1975, which has been included in Section 5.4 Literature References. Although the article is not very clear on the "exogenous CCK" test material actually used, the footnote to Table 1 suggests that the reported half-life data are based on "natural porcine 33-amino acid form of CCK".

This reviewer investigated the literature that the sponsor feedbacked and the literatures we sent them in the labeling comments,
1) Half life of 2.5-3 min is indeed for porcine CCK-33. And only the literature in 1975 has the data for half life, no other literature claimed the half life of CCK.
2) The literatures provided from the Agency are either only mention 2.5-3 min without literature citing, or cited 1975 article.
3) The literature of Krishnamurthy (2003) did mention the half life of CCK-8 in patients with sphincter of Oddi spasm, but the value was 23 ± 16 min which were not the values for normal subjects.
4) The endogenous human CCK half life was suggested to be around 5-7 min (Lancet,

2:826, 1973. No actual data found in the literature, though). However, endogenous CCK is a mixture of CCK-58, 33, 22, 8. Therefore, this half life value cannot be used for CCK-8.

Reviewer's comment: The reviewer recommended to delete the section 12.3 in the label, as currently no solid data are available to claim CCK-8's half life value.

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/s/

JIE CHENG
02/15/2018
The file was replaced to reflect Joette's new comments on DDI section. Thanks.

INSOOK KIM
02/15/2018