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APPLICATION NUMBER:

210850Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210850
Supporting document/s:	001
Applicant's letter date:	August 25, 2017
CDER stamp date:	August 25, 2017
Product:	Sincalide for Injection
Indication:	Stimulation of gallbladder contraction, pancreatic secretion and acceleration of barium meal transit time through small bowel
Applicant:	MAIA Pharmaceuticals, Inc.
Review Division:	DGIEP
Reviewer:	Tamal Chakraborti, PhD
Supervisor:	Sushanta Chakder, PhD
Division Director:	Donna Griebel, MD
Project Manager:	Benjamin P. Vali, MS

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Executive Summary

Introduction

Sincalide is a synthetic octapeptide hormone for parenteral administration. This NDA is a 505(b)(2) application. The Listed Drug is Kinevac® (Sincalide for Injection, 5 µg/vial, NDA 17697). The drug product for this NDA is the same as Kinevac with respect to the active ingredient, dosage form, strength, routes of administration, and indications.

Brief Discussion of Nonclinical Findings

The Applicant did not submit any nonclinical study report in this NDA (no Module 4). The Applicant referred to the label of Kinevac for nonclinical toxicology information.

Recommendations

Approvability

There are no nonclinical approvability issues.

Additional Nonclinical Recommendations

None

Labeling

Nonclinical sections of the proposed draft labeling of Sincalide for Injection conforms to the content and format of labeling for human prescription drug and biological products under 21CFR201.57. However, the following revisions are recommended.

8.1 Pregnancy

Applicant's Version:

8.1 Pregnancy

Risk Summary

(b) (4) In animal embryo-fetal development studies in which sincalide was administered during the period of organogenesis, no effects were seen at doses comparable to the maximum recommended clinical 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 (b) (4) dose on (b) (4)

(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population 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

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 7-13) at doses up to 0.8 times the maximum human dose of 120 ng/kg on a mg/kg 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 6-16, representing 1.0 times the maximum recommended clinical dose on a mg/kg basis. In a separate study at a higher dose of 90 µg/kg administered subcutaneously to CFY rats from Gestation Day 10 through parturition (representing 122 times the maximum clinical doses on a mg/kg basis), offspring showed decreased growth, behavioral changes, and developmental delays. *[see Warnings and Precautions (5)]*.

Evaluation: The Applicant's proposed version appears to be acceptable. However, text of the "Animal Data" was modified in appropriate places to state that the human dose multiples values were based on a body surface area basis.

Recommended Version:

8.1. Pregnancy

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 to 13) at doses up to 0.8 times the maximum recommended human 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 to16, 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

Applicant's Version:

8.2 Lactation

Risk Summary

There are no data regarding the presence of sincalide in human milk, effects on the breastfed infant, or on milk production. (b) (4)

(b) (4)

Data

Animal Data

Direct injection of sincalide in neonatal rats reduced milk consumption with the youngest rats exhibiting the greatest sensitivity to this effect. Although safety margins relative to maternal doses cannot be calculated since rat pups were injected directly, the safety margin in the youngest rat pups was less than 0.1 on a mg/kg bases compared to the maximum adult clinical dose. At higher doses administered subcutaneously in neonatal rats, transient behavioral changes and small effects on physical developmental milestones such as ear opening, eye opening, and incisor appearance were observed (at doses 10 to 200-fold higher than the maximum (b) (4) *[see Warnings and Precautions (5)]*.

Evaluation: Since there are no animal data on the excretion of sincalide into breast milk. The information provided under "Animal Data" in Section 8.2 is not relevant to this section and should be deleted. This information should be incorporated into Section 8.4 Pediatric Use.

Recommended Version: None

8.4 Pediatric Use

Applicant's Version:

8.4 Pediatric Use

Safety and effectiveness in children have not been established.

Evaluation: As mentioned above, the "Animal Data" in Section 8.2 Lactation should be moved from Section 8.2 to Section 8.4 Pediatric Use.

Recommended Version:

Animal Data

Direct injection of sincalide in neonatal rats reduced milk consumption with the youngest rats exhibiting the greatest sensitivity to this effect. Although safety margins relative to maternal doses cannot be calculated since rat pups were injected directly, the safety margin in the youngest rat pups was less than 0.1 on a body surface area bases compared to the maximum adult clinical dose. At higher doses administered subcutaneously in neonatal rats, transient behavioral changes and small effects on physical developmental milestones such as ear opening, eye opening, and incisor appearance were observed (at doses 10 to 200-fold higher than the maximum recommended human dose on a body surface area basis).

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential, or possible impairment of fertility in males or females.

Evaluation: The Applicant's proposed version appears to be acceptable.

Recommended Version: None

Regulatory Background

- Pre-IND Type B meeting was held on March, 2016 to discuss the regulatory pathway to submit a marketing application for Sincalide for Injection, 5 µg/vial.

Studies Submitted

The Applicant did not submit any nonclinical study report in this NDA (no Module 4 information submitted).

Studies Reviewed

N/A

Studies Not Reviewed

N/A

Previous Reviews Referenced

- Pharmacology review of NDA 17697 dated February 24, 1975 by Pierre Des lauriers, Pharmacologist

Integrated Summary and Safety Evaluation

The Applicant did not submit any nonclinical study report in this submission. The Applicant referred to the labeling of Kinevac for nonclinical toxicology information. Please refer to pharmacology review of NDA 17697 dated February 24, 1975 by Pierre Des lauriers, Pharmacologist. Overall, there are no nonclinical approvability issues. In the current review, some labeling changes are recommended.

Appendix/Attachments

None

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/s/

TAMAL K CHAKRABORTI
01/19/2018

SUSHANTA K CHAKDER
01/19/2018