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APPLICATION NUMBER:

210850Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Original NDA
Application Number(s)	NDA 210850
Priority or Standard	Priority
Submit Date(s)	August 25, 2017
Received Date(s)	August 25, 2017
PDUFA Goal Date	February 25, 2018
Division/Office	Division of Gastroenterology and Inborn Errors Products/ODE3/CDER
Reviewer Name	Wen-Yi Gao, M.D., Ph.D.
Team Leader	Stephanie O. Omokaro, M.D.
Review Completion Date	February 14, 2018
Established/Proper Name	Cholecystokinin
(Proposed) Trade Name	Sincalide for injection
Applicant	MAIA Pharmaceuticals
Dosage Form(s)	Oral
Applicant Proposed Dosing Regimen(s)	Adjust doses based on different indications
Applicant Proposed Indication(s)/Population(s)	(1) To stimulate contraction of the gallbladder; (2) To stimulate pancreatic secretion 30 minutes after secretin for injection; (3) To accelerate the transit of a barium meal through the small intestine.
Recommendation on Regulatory Action	Tentative approval
Recommended Indication(s)/Population(s) (if applicable)	Tentative approval

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1. Executive Summary

1.1. Product Introduction

Sincalide is a peptide hormone that has an 8-aminoacid sequence (CCK-8). The Applicant, MAIA Pharmaceuticals Inc., submitted the current 505(b)(2) application to support their product Sincalide for Injection for the following proposed indications:

- To stimulate gallbladder contraction for diagnostic imaging or obtaining gastrointestinal fluids for clinical laboratory analysis;
- To stimulate pancreatic secretion for laboratory analysis;
- To accelerate the transit of a barium meal through the small bowel.

The formulation is intended to be administered as an IV solution of the same dose, concentration, and dosing regimen as that of the listed drug Kinevac (NDA 17697) but considered by the Sponsor to potentially have a positive impact on the recurrent shortages and stability failures that have been associated with Kinevac. The chemistry reviewer has determined that the quality and stability of the proposed drug are equivalent.

Kinevac patent issues:
The drug product patent of Kinevac expires on August 16, 2022. The patent owner, Bracco Diagnostics Inc. filed a patent infringement complaint against the Sincalide NDA Applicant (MAIA) in the Federal District Court of New Jersey. A 30-month stay has been instituted by law with respect to the approval proceeding for NDA 210850. If the Division decides to approve the new 505(b)(2) NDA, this action will at best be a tentative approval until resolution of the ongoing patent litigation.

Kinevac anaphylaxis and vasovagal reactions:
OSE Pharmacovigilance Reviewers (Kimberley Swank, PharmD; Kira Leishear White, Ph.D.) identified 18 cases of postmarketing spontaneous reports from FDA Adverse Event Reporting System (FAERS). They classified these adverse events as “anaphylactic reactions” and “vasovagal reactions”. OSE recommended adding “anaphylaxis, hypersensitivity reaction, and vasovagal reactions” to the Warnings and Precautions section of the Kinevac label.

Safety concerns of CCK-8 (Kinevac and Sincalide):

(1) CCK-8 is the most abundant neuropeptide in the brain; and it has temporal lobe epilepsy maps matched in at least 8 animal models (Wyeth, 2012; Clynen, 2014; Dobolyi, 2014; Eser, 2005; Banks 1996; Sugiyama, 2003; Gall, 1988_1; Gall, 1988_2). These animal studies showed that CCK can enter blood brain barrier causing clonic convulsion and seizures that are different from anaphylaxis. Anaphylaxis signs and symptoms (upper airway congestion, lower airway spasm, hypotension, tachycardia, flushing, urticaria, or diarrhea) were absent.
(2) CCK-8 can be rapidly degraded by plasma aminopeptidases (Koulischer, 1982). However, the degradation products, CCK-4 and gastrin (sharing the C-terminal 5 peptides), remain neurologically active (Banks 1996; Sugiyama, 2003).

Postmarketing seizure and clonic convulsion adverse events of Kinevac:
Among the 18 OSE-cases, 7 patients/cases had isolated seizures, epilepsy, clonic convulsion, cardio-respiratory arrest, high blood pressures, pupil fixed, syncope, and/or loss of consciousness, immediately after the Kinevac IV injection at Nuclear Medicine Departments. Because these patients did not have anaphylactic signs such as conjunctival injection, nasal congestion, laryngeal edema, bronchospasm tachypnea, tachycardia, hypotension, flushing, urticaria, or diarrhea, the DGIEP clinical reviewer believes that these clinical manifestations are not the result of anaphylactic reactions. Kinevac IV injection-induced CNS dysfunction cannot be ruled out.

1.2. Conclusions on the Approvability

In summary, Sincalide carries the same benefit-risk potential as Kinevac. It is a candidate with potential positive impact on the drug shortage program and is granted priority review. On the other hand, as a CCK-8 family member, it can enter blood-brain barrier and interferes with CNS activity. This potential risk has not been evaluated in this submission. The clinical reviewer recommends Tentative Approval of Sincalide for the proposed indications. In addition, the potential seizure risk should be added to Section 6 of Sincalide label.

1.3. Benefit-Risk Assessment

This 505(b)(2) New Drug Application (NDA) is based on FDA's previous findings on safety and efficacy of the Listed Drug, Kinevac (Sincalide) for Injection.

MAIA conducted a literature research and summarized the clinical efficacy of the listed drug Kinevac. Fifteen articles were identified, which provides information for utility of Sincalide in a variety of related and unrelated indications. Several diagnostic applications have been evaluated, including predicting bile duct distention post-cholecystectomy, evaluating gallbladder physiologic dysfunction, and in the aid of endoscopic retrograde cholangiopancreatography. In addition, a number of treatment approaches using Sincalide have been reported, including use in parenteral nutrition-associated cholestasis, chemotherapy-related ileus, and the treatment of psychotic symptoms in patients with chronic schizophrenia.

Medical Officer Comments:
The clinical reviewer agrees that the listed drug Kinevac has been used extensively for diagnostic purposes and for some medical treatments. The benefit-risk assessment of Sincalide for injection is similar to Kinevac. Sincalide for injection can be used to address the drug-shortage program.

1.4. Patient Experience Data

No clinical data submitted

2. Therapeutic Context

2.1. Analysis of Condition

CCK will be used for diagnostic purposes:

- To stimulate gallbladder contraction: For example, HIDA Scan (Hepatobiliary Iminodiacetic Acid Scan) with CCK. By adding CCK, it stimulates the gallbladder to contract allowing to see how well it is functioning. Aspiration of bile sample for laboratory analyses;
- To stimulate pancreatic secretion (usually in combination with secretin) for analysis of pancreatic exocrine enzyme activity, composition, and cytology;
- To accelerate the transit of a barium meal through the small bowel to decrease the time and extent of radiation associated with x-ray examination of the intestinal tract.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Sincalide for injection seeks the 505(b)(2) regulatory pathway for the approval. It is not marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Development of Sincalide for injection was under pre-IND 129160:

- On January 26, 2016, the Applicant (MAIA Pharmaceuticals) submitted a pre-IND meeting request to discuss the regulatory pathway of Sincalide for injection, 5 mcg/vial.
- The Pre-IND meeting was held on March 29, 2016. The Division agreed that a 505(b)(2) application is acceptable. The Division also agreed that there are no novel inactive ingredients in MAIA's formulation.
- The NDA was submitted on August 25, 2017. There was no clinical safety and efficacy data submitted in the NDA.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI audit was not conducted.

4.2. Product Quality

OPQ joint review recommended approval of this NDA, and commented "The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product."

4.3. Clinical Microbiology

Clinical microbiology study was not conducted.

4.4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology was reviewed by Drs. Tamal Chakraborti and Sushanta Chakder. There are no nonclinical approvability issues.

4.5. Clinical Pharmacology

The submitted clinical pharmacology information was reviewed by Drs. Jie Cheng and Insook Kim. The Applicant did not conduct an *in vivo* bioequivalence study but requested a biowaiver for the relative BA/BE study between the listed drug and Sincalide for injection. A biowaiver was granted as the final drug concentration prior to injection, and the dosing instruction are the same between Kinevac and Sincalide for injection and there are no clinical pharmacology-related concerns.

5. Sources of Clinical Data and Review Strategy

There is no clinical data of Sincalide submitted to support this NDA. There is no safety data submitted for the listed drug Kinevac. Upon DGIEP request, OSE conducted postmarketing spontaneous reports of Kinevac in FAERS (FDA Adverse Event Reporting System). The FAERS search period was from July 21, 1976 to March 25, 2016. The OSE review was reported to DARRTS on May 18, 2016.

Review Strategy

- To evaluate the 18 FAERS AE cases provided by OSE and to identify 7 of the patients who had isolated seizures, epilepsy, clonic convulsion, cardio-respiratory arrest, high blood pressures, pupil fixed, syncope, and/or loss of consciousness, immediately after the Kinevac IV injection in operating rooms.
- To confirm through published literature that CCK-8 is the most abundant neuropeptide in the brain; and that it has temporal lobe epilepsy maps matched in at least 8 animal models (Wyeth, 2012; Clynen, 2014; Dobolyi, 2014; Eser, 2005; Banks 1996; Sugiyama, 2003; Gall, 1988_1; Gall, 1988_2). These animal studies showed that CCK can enter blood brain barrier causing clonic convulsion and seizures that are different from anaphylaxis. Anaphylaxis signs and symptoms (upper airway congestion, lower airway spasm, hypotension, tachycardia, flushing, urticaria, and diarrhea) were absent.
- To confirm that CCK-8 can be rapidly degraded by plasma aminopeptidases (Koulischer, 1982). However, the degradation products, CCK-4 and gastrin (sharing the C-terminal 5 peptides), remain neurologically active (Banks 1996; Sugiyama, 2003).

6. Review of Relevant Individual Trials Used to Support Efficacy

No clinical data submitted

7. Integrated Review of Effectiveness

No clinical data submitted

8. Review of Safety

8.1. Safety Review Approach

No new safety data were submitted using the proposed drug product.
The safety review is based on OSE review (DARRTS, May 18, 2016) and FAERS case reports from July 21, 19976 to March 25, 2016 (DARRTS, May 18, 2016).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

No clinical data submitted

8.2.2. Relevant characteristics of the safety population:

No clinical data submitted

8.2.3. Adequacy of the safety database:

No clinical data submitted.
OSE identified 18 postmarketing AE cases from FAERS (DARRTS, May 18, 2016).

8.3. Safety Results

The Division of Pharmacovigilance-I (DPV-I) conducted a search of the FAERS database from July 21, 1976 through March 25, 2016 that yielded 119 reports with Kinevac. Of the 119 reports, 22 reported a serious outcome of death, life-threatening event, hospitalization or disability. There were two death cases; one case was determined to be unrelated to Kinevac administration and the other case described a patient who developed an anaphylactic reaction, severe respiratory depression, and cardiac arrest following Kinevac administration. Of the 119 reports, unlabeled adverse events included anaphylaxis (n=12), seizures (n=8), and hypersensitivity reactions (n=6).

All 8 cases of seizures demonstrated a temporal association with Kinevac. Seizures occurred approximately 2-35 minutes after receiving Kinevac. DPV-I plans to continue monitoring for reports of seizures with Kinevac.

DGIEP clinical reviewer reviewed some of the anaphylactic or vasovagal reaction cases, and found at least 7 cases that did not have anaphylactic manifestations. Kinevac-induced CNS dysfunction cannot be ruled out:

- Case #3269746 (Case Report page 3): A 30-year-old male had 3 seizure episodes a day for the past 8 days following administration of Kinevac on April 19, 1999 while in the Nuclear Medicine Department (DGIEP MO: *anaphylaxis does not have repeated seizures episodes*). During the seizure episode, the patient experienced an increase in blood pressure and severe shaking (DGIEP MO: *vasovagal syncope does not increase blood pressure*). The patient did not respond to anti-allergic medication Benadryl, but was improved with continuous infusion of Dilantin (anti-epileptic treatment).

- Case #3324866 (Case Report page 6): A patient (age unknown) developed clonic convulsion, depressed level of consciousness, hydrocephalus, hypertension and hypotension following administration of Kinevac in the Nuclear Medicine Department (DGIEP MO: *CCK induced clonic convulsion, depressed consciousness, hypertension, and hydrocephalus cannot be ruled out. These clinical manifestations are not associated with vasovagal reactions or anaphylaxis*.)
- Case #4153278 (Case Report page 13): A 35-year-old male experienced loss of consciousness and hypertension following administration of Kinevac (DGIEP MO: *Vasovagal reaction is not associated with hypertension. The patient did not have conjunctival injection, nasal congestion, laryngeal edema, bronchospasm tachypnea, tachycardia, hypotension, flushing, urticaria, or diarrhea.*)
- Case #4656866 (Case Report page 22): A 82-year-old female experienced hypotension, hypoventilation and stupor following administration of Kinevac (DGIEP MO: *The cause of mental status changes and stupor are unclear. CCK-induced mental status changes cannot be ruled out. The patient did not have conjunctival injection, nasal congestion, laryngeal edema, bronchospasm tachypnea, tachycardia, hypotension, flushing, urticaria, or diarrhea.*)
- Case #4786297 (Case Report page 26): A 26-year-old female had clonic convulsion, paresthesia, speech disorder, and tongue edema following administration of Kinevac (DGIEP MO: *The cause of clonic convulsion, paresthesia and speech disorder is unclear. CCK-induced CNS reactions cannot be ruled out. The patient did not have conjunctival injection, nasal congestion, laryngeal edema, bronchospasm tachypnea, tachycardia, hypotension, flushing, urticaria, or diarrhea.*)
- Case #5336968 (Case Report page 30): A 35-year-old male experienced hypotension and seizure following administration of Kinevac. (DGIEP MO: *CCK-induced CNS reactions cannot be ruled out. The patient did not have anaphylactic signs such as conjunctival injection, nasal congestion, laryngeal edema, bronchospasm tachypnea, tachycardia, hypotension, flushing, urticaria, or diarrhea.*)
- Case #5846560 (Case Report page 32): A 9-year-old male experienced seizures and jerking of the arms, legs and shoulders following administration of Kinevac. (DGIEP MO: *CCK-induced myoclonus and seizures cannot be ruled out. The patient did not have anaphylactic signs such as conjunctival injection, nasal congestion, laryngeal edema, bronchospasm tachypnea, tachycardia, hypotension, flushing, urticaria, or diarrhea.*)

In summary, FDA FAERS database identified multiple isolated seizure/epilepsy, clonic convulsion, cardio-respiratory arrest, high blood pressures, pupil fixed, syncope, and/or loss of consciousness. These cases did not have clinical signs and symptoms of anaphylaxis or vasovagal reactions. Misdiagnosis of CCK-associated seizure/epilepsy and clonic convulsion may lead to a life-threatening delay of medical treatments.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultations was held.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling underwent extensive negotiations between the Applicant and FDA. See the final negotiated labeling. "Seizures" was added to the Adverse Reactions section of the label, in addition to the terms for anaphylaxis and vasovagal reactions proposed by OSE.

10.2. Nonprescription Drug Labeling

Sincalide is a prescription drug product and nonprescription drug labeling is not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

REMS was not recommended.

12. Postmarketing Requirements and Commitments

There were no post marketing requirements recommended. Two CMC PMCs were recommended:

PMC #1 Description:
Assay and Uniformity of Dosage Units (UoD) data for the first 10 commercial batches.

PMC #2 Description:
For at least the first three commercial batches, perform the following testing during process validation:

a. Determination of Assay on lyophilized vials as per the test method using vials (b) (4) (b) (4) to confirm product uniformity. (b) (4) (b) (4) (b) (4)
b. Determination of UoD on 10 (or 30) individual lyophilized vials per batch collected at random from the beginning, middle, and end of the filling operation.

13. Appendices

13.1. References

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13.2. Financial Disclosure

No clinical data submitted.

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/s/

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02/21/2018

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02/21/2018