CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210850Orig1s000

SUMMARY REVIEW

Division of Gastroenterology

Clinical/Signatory Summary Review

Established Product Name: Sincalide for Injection

Submission: NDA 210850

Applicant: Maia Pharmaceuticals, Inc.

Submission date: September 26, 2022

PDUFA Goal Date: November 25, 2022

Review Completion Date: November 22, 2022

Proposed Indication(s):

- 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 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.

Dosage Form: 5mcg lyophilized cake or powder in a single dose vial for reconstitution

Reviewer: Tara Altepeter, MD, Associate Director for Therapeutic Review, DG

Recommended Action: Approval

Background:

On February 23, 2018, Maia Pharmaceuticals (the Applicant) received a tentative approval for NDA 210850 for Sincalide for Injection (5mcg/vial), under 21 CFR 314.105. The tentative approval provided 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 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.

At that time, the tentative approval was issued because the application relied upon the listed drug Kinevac, which was subject to patient protection. Further, the patent holder had initiated a patent

infringement suit (patent 6,803,046) in the United States District Court for the District of New Jersey (Docket no. 3:17-cv-13151). Thus, a final approval could not be issued at that time.

The Applicant was advised that final approval could not be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
   b. the date the court decides that the patent is invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,
   c. the listed patent has expired, and

2. FDA is assured there is no new information that would affect whether final approval should be granted.

Current Submission:

On September 26, 2022, the Applicant resubmitted NDA 210850 with request for final approval. The application includes the following (described further below).

1) Confirmation of patent expiration
2) Product Quality Information
3) Safety Update Report
4) Proposal for use of an alternate (b) (4) vial.
5) Updated labeling

1) Confirmation of patent expiration:

The patent for the listed drug, Kinevac (patent no. 6,803,046), expired on August 16, 2022, per the Orange Book.

2) Stability Data Update

The Applicant provided updated stability data for 3 registration batches to 24 months when stored at room temperature conditions. The drug product reviewer concluded that the results continue to meet the product specification, and the proposed expiration dating period of 24 months is acceptable. See OPQ review by Zhengfang Ge dated November 7, 2022.

In addition, the Applicant provided a reference to previously submitted information (sequence #3, received November 17, 2017) to justify the hold time of 8 hours at room temperature, after reconstitution. The microbiology reviewer (Dustin Thomas) confirmed this to be acceptable.

3) Safety Update Report:

Since the tentative approval was issued in 2018, no new safety concerns have been identified. No new clinical trials were conducted during this timeframe with sincalide. The applicant conducted a search of FDA's FAERS database, as well as a literature review, neither of which identified new safety concerns.

Additionally, the Division of Pharmacovigilance (DPV-I) conducted an independent review of FAERS data for adverse events reported between March 26, 2016 (date of last DPV search) and October 23, 2022. The DPV reviewer concluded that no new safety signals were identified that warranted inclusion in labeling. See detailed review by Michelle Hines, dated November 3, 2022.

The applicant submitted (in response to FDA's information request dated October 21, 2022) a statement confirming that a recent literature search was conducted regarding the use of sincalide in pregnant and lactating women, and that the information included in the Prescribing Information (PI) accurately describes the available literature. No new information was identified that changes the benefit/risk profile of sincalide when used in pregnant or lactating women since the PI was drafted in the last review cycle.

4) Proposal for use of an alternate (b) (4) vial

In this resubmission, the Applicant proposed introduction of an alternative USP (b) (4) glass vial with (b) (4) feature for the packaging of the drug product. The Office of Pharmaceutical Quality (OPQ) review team determined that the change could not be approved at this time as there were inadequate data provided to support the change (including, but not limited to, lack of at least one batch of drug product packaged in the proposed alternate container/closure system with a minimum 3 months stability data at long term and accelerated storage conditions).

The OPQ team sent an information request to the Applicant on October 3, 2022 requesting additional details and justification for the proposed changes. On October 4, 2022, the Applicant responded with submission of a comparability protocol (CP) for the alternate container/closure system. The OPQ team concluded that the CP could not be approved due to insufficient data. The Applicant formally withdrew the comparability protocol and all relevant sections pertinent to the proposed alternate container/closure system from the resubmission (response to information request, received October 25th).

(b) (4)

5) Labeling:

The following changes were made to the previously agreed-upon prescribing information:

Deletions shown as strike-through, new text has double underline/bold.

Product Title in Highlights:

SINCALDE ~~FOR INJECTION~~ **for injection,** for intravenous use

Section 16:

- Store at **20°C to** 25°C (**68°F to** 77°F); excursions permitted to 15**°C to** 30°C (59**°F to** 86°F) [See USP Controlled Room Temperature].

The change to the product title was made to follow the Product Title guidance.[1]

The changes to section 16 were minor for clarity of appropriate range of storage temperatures per USP <1079>.

Additionally, changes were recommended to the container/carton label for clarity and to improve readability (see labeling review by Sherly Abraham, dated November 4, 2022). The Applicant revised the container/carton label, and the version received on November 21, 2022 is considered acceptable.

Conclusion/Recommendations:

The application is recommended for approval.

[1] https://www.fda.gov/media/110453/download

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/s/

TARA A ALTEPETER
11/22/2022 12:23:00 PM

Cross-Discipline Team Leader Review
Division Director Summary Review

Date	February 23, 2018
From	Joette M. Meyer, PharmD, CDTL Joyce Korvick, MD, MPH, Deputy Director for Safety Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader and Division Director Review
NDA/BLA # and Supplement#	NDA 210850
Applicant	MAIA Pharmaceuticals, Inc.
Date of Submission	August 25, 2017
PDUFA Goal Date	February 25, 2018
Proprietary Name	none
Established or Proper Name	sincalide
Dosage Form(s)	Injection: Single dose vial containing 5 mg of sincalide as a lypophilzed power for reconstitution
Applicant Proposed Indication(s)/Population(s)	Sincalide for Injection may be used: (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.
Applicant Proposed Dosing Regimen(s)	• For prompt contraction of the gallbladder, a dose of 0.02 mcg sincalide per kg (1.4 mcg/70 kg) is injected intravenously over a 30- to 60-second interval; if satisfactory contraction of the gallbladder does not occur in 15 minutes, a second dose, 0.04 mcg sincalide per kg, may be administered. To reduce the intestinal side effects, an intravenous infusion may be prepared at a dose of 0.12 mcg/kg in 100 mL of Sodium Chloride Injection USP and given at a rate of 2 mL per minute; alternatively, an intramuscular dose of 0.1 mcg/kg may be given. • For the Secretin-sincalide test of pancreatic function, the patient receives a dose of 0.25 units secretin per kg by intravenous infusion over a 60-minute period.

	Thirty minutes after the initiation of the secretin infusion, a separate IV infusion of sincalide at a total dose of 0.02 mcg per kg is administered over a 30-minute interval. For example, the total dose for a 70 kg patient is 1.4 mcg of sincalide; therefore, dilute 1.4 mL of reconstituted sincalide solution to 30 mL with Sodium Chloride Injection USP and administer at a rate of 1 mL per minute. • To accelerate the transit time of a barium meal through the small bowel, administer sincalide after the barium meal is beyond the proximal jejunum. The recommended dose is 0.04 mcg sincalide per kg (2.8 mcg/70 kg) injected intravenously over a 30- to 60- second interval; if satisfactory transit of the barium meal has not occurred in 30 minutes, a second dose of 0.04 mcg sincalide per kg may be administered. For reduction of side effects, a 30-minute IV infusion of sincalide [0.12 mcg per kg (8.4 mcg/70 kg) diluted to approximately 100 mL with Sodium Chloride Injection USP] may be administered.
Recommendation on Regulatory Action	Tentative Approval
Recommended Indication(s)/Population(s) (if applicable)	Sincalide for Injection is indicated to: (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 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.
Recommended Dosing Regimen(s) (if applicable)	Same as above, with information removed on the intramuscular route of administration (see Background) below.

EDR Location: \\CDSESUB1\evsprod\NDA210850\210850.enx
Associated PIND: 129160

Core Review Team (TL / Reviewer)	
Clinical	Stephanie Omokaro / Wen-Yi Gao
Nonclinical	Sushanta Chakder / Tamal Chakraborti
Product Quality	Application Technical Lead (ONDP): Hitesh Shroff Drug Substance/Labeling (ONDP): Donna Christner / Joseph Leginus Drug Product/Environmental Assessment (ONDP): Moo-Jhong Rhee / Zhengfang Ge Process (OPF): Nallaperumal Chidambaram / Yaodong Huang Facilities (DIA): B.J. Ryan / Vidya Pai Microbiology (DMA): Erika Pfeiler / Paul Dexter Biopharmaceutics (ONDP): Tien Mien Chen / Bryan Ericksen
Clinical Pharmacology	Insook Kim / Jie Cheng
DMEPA	Sarah Vee / Sherly Abraham
DPV I	Lisa Harinstein / Ivone Kim
Consultants (TL / Reviewer)	
DMIP	Nushin Todd / Brenda Ye
DPMH / Maternal Health Team	Miriam Dinatale / Catherine Roca
OPDP	Kathleen Klemm / Meeta Patel

1. Benefit-Risk Assessment

Sincalide for Injection is a 505(b)(2) NDA from MAIA Pharmaceuticals, Inc. which references Kinevac (sincalide) for Injection (NDA 17697, approved July 21, 1976) as the listed drug (LD). The application is based, in part, on the Agency's findings of safety and effectiveness for Kinevac. The proposed product has the same active ingredient (sincalide), dosage form (injectable), strength (5 mcg per vial), route of administration (intravenous) and indications as the LD, Kinevac.

Sincalide is a is a synthetic octapeptide and a cholecystokinin analog (CCK-8). Cholecystokinin is the major hormone responsible for gallbladder contraction and pancreatic enzyme secretion. It also stimulates intestinal motility. Sincalide is used as an intravenous injection to stimulate gallbladder contraction, pancreatic secretion and accelerate transit of a barium meal through the small bowel for assessment with various diagnostic imaging modalities.

The application was granted a priority review because of recurrent shortages of Kinevac and the lack of other approved products for the labeled indication. Kinevac has been listed in the FDA Drug Shortages Database since March 01, 2017[1] and was previously listed from June 2013 until December 2015. The proposed product was developed to provide an alternative source of drug to patients for this unmet medical need. In addition, the applicant is proposing a 24-month shelf life for their product citing stability failures with the current formulation of Kinevac and a reduced shelf life of 15 months. The most recent CMC approval for Kinevac (NDA 17697/S-030, March 1, 2017) extends the 15-month shelf life to 21 months. The OPQ review has agreed to the 24-month expiry dating of this sincalide product.

The applicant has cited the following information to serve as the scientific bridge between the proposed product and Kinevac:

- Same active ingredient in the same concentration (b) (4) (b) (4)

- Same inactive ingredients in the same concentrations except for potassium phosphate dibasic (9 mg) and polysorbate 20 (0.005 mcg) in Kinevac, which are not present in the proposed drug product. Polysorbate 20 is (b) (4) and its absence has no impact on solubility of the active ingredient. Both drug products are true solutions after reconstitution and/or dilution. The difference in the final inactive concentrations between the two products after reconstitution for intravenous injection is below (b) (4) and even lower after dilution for intravenous infusion. Such small differences are unlikely to impact bioavailability or change the pharmacokinetic profile of the drug.

[1] Drug Shortages Database: https://www.accessdata fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Sincalide%20(Kinevac)%20Lyophilized%20Powder%20for%20Injection&st=c

- Similarity of physicochemical characteristics (pH and osmolality) of the two drug products.

The OPQ team reviewed this data and concurred. They concluded neither potassium phosphate dibasic or polysorbate 20 are required for [redacted] (b) (4) the active ingredient, and therefore their absence is unlikely to affect bioavailability and granted the applicant's request for a waiver from conducting an *in vivo* bioavailability/bioequivalence (BA/BE) study for the intravenous route of administration. The applicant's scientific bridge was found acceptable.

No new clinical efficacy data were submitted. The safety information for sincalide was updated using postmarketing spontaneous reports of serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, vasovagal reactions (e.g. dizziness, loss of consciousness, nausea, diaphoresis, syncope and hypotension) and seizures.

The review team recommends approval for this application. However, due to ongoing legal litigation, as described below, a tentative approval is recommended until the legal action is resolved.

2. Background

During the review cycle, several legal and regulatory issues emerged and were addressed as follows:

Patent Infringement
The applicant submitted a paragraph IV patent certification acknowledging US Patent No. 6,803,046 (set to expire on August 16, 2022), held by the holder of NDA 17697 (Bracco Diagnostics Inc.) for Kinevac. The applicant stated "the patents is invalid, unenforceable and/or will not be infringed by the manufacture, use or sale" of their product. As required by 21 CFR 314.52(b), the applicant notified Bracco of their NDA submission. Bracco subsequently filed a patent infringement complaint against the applicant in the Federal District Court of New Jersey. This filed patent infringement complaint (blocking petition) was executed during the appropriate timelines, as defined by statute and corresponding regulation, as confirmed by the applicant. Consequently, unless there is an out of court settlement or if the court rules in favor of MAIA beforehand, a 30-month stay has been instituted. Therefore, the FDA 505(b)(2) review committee recommended that if an approval were recommended by the review team, it could only be a tentative approval until the legal action is resolved.

Citizen Petitions
The original formulation of Kinevac is the subject of two ongoing citizen petitions. The formulation of Kinevac approved in 1976 was marketed until November 27, 2002, when a reformulated product was approved. The 1976 formulation of Kinevac consisted of the active ingredient (i.e., sincalide) and sodium chloride as an inactive ingredient. The 2002 formulation, which is the currently approved formulation, contains mannitol, arginine hydrochloride, lysine hydrochloride, methionine, pentetic acid, sodium metabisulfite, potassium phosphate dibasic, and polysorbate 20 as inactive ingredients. Sodium chloride was

removed as an inactive ingredient. The above-mentioned patent (6,803,046) applies to the 2002 formulation.

The following information comparing the formulations for Kinevac and the applicant's proposed drug product was provided by OPQ (Hitesh Shroff in an email dated December 5, 2017):

- The original (1976) Kinevac formulation only contained sincalide, sodium chloride, water and pH was adjusted with HCl or NaOH.
- In 2002, Kinevac was reformulated to remove sodium chloride and replace it with mannitol. In addition, L-arginine HCl, L-Lysine HCl, L-Methionine, Pentetic acid, Sodium Metabisulfite, Potassium phosphate dibasic and polysorbate 20 were added.
- The proposed sincalide drug product does not contain potassium phosphate dibasic and polysorbate 20 compared to the 2002 Kinevac formulation.

Kinevac and Proposed Sincalide Injection Formulations

Ingredient	Function	Proposed Sincalide Injection Quantity/ Vial	LD Kinevac August 2002 Reformulation Quantity/Vial	LD Kinevac 1976 ORIGINAL Quantity/Vial
Sincalide	Active	5 mcg	5 mcg	5 mcg
Sodium Chloride	(b) (4)	-	-	(b) (4)
Mannitol		170 mg	170 mg	-
L-Arginine hydrochloride		30 mg	30 mg	-
L-Lysine hydrochloride		15 mg	15 mg	-
L-Methionine		4 mg	4 mg	-
Pentetic acid		2 mg	2 mg	-
Sodium Metabisulfite		0.04 mg	0.04 mg	-
Sodium Hydroxide	pH adjusting agent	Q.S. for pH Adjustment	Q.S. for pH Adjustment	Q.S. for pH Adjustment
Hydrochloric Acid	pH adjusting agent	Q.S. for pH Adjustment	Q.S. for pH Adjustment	Q.S. for pH Adjustment
Potassium phosphate dibasic	(b) (4)	-	9 mg	-
Polysorbate 20		-	(b) (4)	-

Ingredient	Function	Proposed Sincalide Injection Quantity/ Vial	LD Kinevac August 2002 Reformulation Quantity/Vial	LD Kinevac 1976 ORIGINAL Quantity/Vial
Water for Injection†	(b) (4)	(b) (4)		

The first citizen petition (Docket ID: FDA-2017-P-1297) was submitted on behalf of Regcon Solutions on March 2, 2017 to determine whether the original formulation is suitable for submission as an Abbreviated New Drug Application (ANDA).

The second citizen petition (Docket ID: FDA-2017-P-6805) was submitted on behalf of Bracco (the manufacturer of Kinevac) on December 12, 2017 to determine the original formulation was discontinued due to reasons of safety and effectiveness.

The Office of Regulatory Policy has concluded that an action on the current applicant is not affected by these two pending citizen petitions.

Intramuscular Route of Administration

Upon review of the latest annual report for Kinevac (dated August 31, 2017) it was determined that the Dosage and Administration section of the PI provided for an alternative route of administration (intramuscular), in addition to the approved intravenous route of administration. Upon discussion with Bracco, it was determined that the statement has been inadvertently included in the Kinevac PI since March 1988. No data were ever submitted in support of this route of administration; nor was it addressed in the NDA submission supporting the reformulation in 2002. Bracco submitted a Changes Being Effected (CBE) labeling supplement on February 1, 2018 with the statement removed and the revised PI was approved February 9, 2018.[2]

Therefore, while the applicant's NDA included reference to the intramuscular route of administration in their proposed PI, it was removed during the review and will not be addressed further.

3. Product Quality

Sincalide for Injection is a sterilized lyophilized white to off-white cake or powder to be reconstituted for intravenous injection. The proposed drug product and the current formulation of the LD (Kinevac), approved in 2002, are identical in the dosage form and strength. However, there are differences between the formulations of the proposed product and the LD,

[2] Kinevac PI, dated 2/9/18: https://www.accessdata fda.gov/drugsatfda_docs/label/2018/017697s031lbl.pdf

as discussed below. The proposed sincalide drug product does not contain potassium phosphate dibasic and polysorbate 20 compared to the 2002 Kinevac formulation.

The OPQ review concludes:

- *Drug Substance*: The data are adequate to support the use of sincalide drug substance in the manufacture of sincalide for injection drug product. The drug substance used for the proposed sincalide for injection drug product is obtained from (b) (4) (b) (4) (b) (4) (b) (4)

  Drug Product: The applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product for intravenous administration. Based on long-term and accelerated stability data of the drug product assuring the identity, strength, purity and quality, a 24-month of expiration dating period when stored between 20ºC to 25ºC in the proposed container closure system is granted.

- *Biopharmaceutics*: The applicant's request for a waiver from conducting an *in vivo* bioavailability/bioequivalence (BA/BE) study for the intravenous route of administration was granted. Neither inactive ingredients of potassium phosphate dibasic or polysorbate 20 are required for (b) (4) the active ingredient, and therefore their absence is unlikely to affect bioavailability. Therefore, the waiver is justified via a biobridge pathway under 21 CFR 320.24 (b)(6).

  CDTL Comment: The biowaiver is not applicable to the intramuscular route of administration and the Biopharmaceutics recommendation for approval only applies to the intravenous route of admonition. However, as discussed in Section 2 Background, the intramuscular route of administration was removed from labeling during the review cycle and is no longer a concern.

- *Microbiology:* The environmental monitoring at (b) (4) manufacturing process buildings/facilities, component/ equipment sterilization, bulk drug product (b) (4) (b) (4) as well as the microbiology-related attributes in the drug product specification including bacterial endotoxins, sterility and container closure integrity, etc. were found acceptable and the NDA is recommended for approval based on sterility assurance.

- *Categorical Exclusion for the Environmental Assessment*: Granted

- *Office of Process and Facilities*: Approval recommendation for the facilities involved in this application

  - The drug substance is manufactured, packaged and undergoes analytical testing at (b) (4) This site has extensive familiarity with peptides and there have been multiple inspections at this site; most recently in (b) (4) with no inspectional observations issued. Control testing

is performed at (b) (4) Recent inspections at this site in (b) (4) were VAI and NAI.

- The drug product is manufactured, packaged, tested and released at Gland Pharma Ltd., Hyderabad, India. The Process review notes that the firm has used overage of active and overfill, which presents scale-up risks that may present themselves at the (b) (4) scale and may not be readily apparent at the (b) (4) exhibit batch scale. Therefore, a post-approval inspection is recommended to support this NDA to review the firm's validation activities and ensure that the selected manufacturing process delivers the critical quality attributes for the drug product. See Section 12 Labeling, Post-Marketing Commitments (PMCs).

- *Labeling*: The CMC sections of the revised PI, carton and container labeling submitted on February 12, 2018 are acceptable.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted with this application. Reference is made to the Prescribing Information (PI) of Kinevac, the listed drug, for nonclinical toxicology information.

5. Clinical Pharmacology

An *in vivo* bioequivalence study was not conducted and the applicant requested a biowaiver from conducting a 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 the proposed product.

See Section 12 Labeling for additional discussion regarding drug interactions and pharmacokinetics.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No new clinical studies were submitted with this application. The application is based, in part, on the Agency's findings of safety and effectiveness for Kinevac (NDA 17697).

The applicant conducted a literature search, to summarize the existing efficacy information for sincalide since the approval of Kinevac. The clinical reviewer agrees that sincalide has been used extensively in patients for various diagnostic purposes.

8. Safety

The application is based, in part, on the Agency's findings of safety and effectiveness for Kinevac (NDA 17697). The applicant conducted search of the published literature and the FDA Adverse Event Reporting System (FAERS) between 1976 through 2013 to summarize the existing safety information for sincalide since the approval of Kinevac. The applicant concluded that the postmarketing safety information provided in published literature and from the FAERS database did not identify new information for inclusion in the proposed labeling.

CDTL Comment: It is not clear why the applicant chose an end date of 2013.

The Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance-I (DPV-I) conducted a safety review of postmarketing spontaneous reports for sincalide reported to FAERS between July 21, 1976 (the approval date of Kinevac) and March 25, 2016 (NDA 17697 by Kimberly Swank, dated May 18, 2016 in DARRTS). The clinical reviewer also reviewed the FAERS reports. See additional discussion in Section 12 Labeling (Warnings and Precautions and Adverse Reactions).

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

No new information on pediatrics was reviewed. The LD does not have a pediatric indication.

The proposed product has the same active ingredient, indication, dosage form, dosing regimen, and route of administration as the LD; therefore, PREA is not triggered.

11. Other Relevant Regulatory Issues

No new clinical information was submitted with this application; therefore, no clinical inspections were conducted.

12. Labeling

The review team reviewed the approved PI for the LD, Kinevac, which is in non-Physician Labeling Rule (PLR) format and further ensured that the proposed sincalide PI aligned with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR) formats, current labeling regulations (21 CFR 201.57), PLR labeling guidances, the Selected Requirements for Prescribing Information (SRPI), and best labeling practices.

Below is a summary of the substantive issues in the PI discussed during the review. Comments from the review team and consultants were incorporated. OPDP did not have any comments on the PI.

Discussion of the content of the PI for the proposed product is based upon a comparison to the currently approved PI for Kinevac (dated February 9, 2018), unless otherwise noted.

PRESCRIBINIG INFORMATION
HIGHLIGHTS

In general, revisions to this section were made in alignment with the revisions in the Full Prescribing Information and will not be described here.

The Product Title line is as follows. There is no proposed nonproprietary name.

SINCALIDE FOR INJECTION, for intravenous use

The applicant's proposed Established Pharmacologic Class (EPC) was (b) (4) (b) (4) As per the FDA EPC Text Phrase database,[3] the correct EPC for sincalide is "cholecystokinin (CCK) analog."

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

The indications were not revised, with the exception that the age group for the indicated populations (adults) was added and the indication for pancreatic secretion was made clear that sincalide and secretin are used in combination (30 minutes apart, as described in the Dosage and Administration section) to achieve the desired effect.

A consult review from the Division of Medical Imaging Products (DIMP) confirmed the indications are up-to-date and consistent with current clinical practice and "diagnostic imaging" is broad term that encompasses various modalities used in practice to stimulate gallbladder contraction and pancreatic secretion, including (b) (4) fluoroscopy, (b) (4)

Sincalide for Injection is indicated 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;
- to stimulate pancreatic secretion (b) (4) in combination with secretin) prior to obtaining a duodenal aspirate for analysis of enzyme activity, composition, and cytology;

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3 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM428333.pdf

- 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration Instructions

Information on the recommended dosage was relocated to the top of this section and the dosing information by indication organized into a table for ease of reading, as shown below. As noted earlier, reference to an intramuscular route of administration is not included.

DIMP also agreed with the review team that the following information on the practice of (b) (4) is outdated and likely reflected the practice before dynamic imaging in (b) (4) became available. This information was deleted from the PI.

(b) (4)

Table 1: Recommended Adult Dosage and Administration of Sincalide for Injection by Treatment Indication

Indication	Sincalide for Injection Dosing and Administration Instructions
To stimulate contraction of the gallbladder	Sincalide for Injection 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. Alternatively, Consider an 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 in combination with secretin for injection	Secretin for Injection: 0.25 units/kg as intravenous infusion over 60 minutes Sincalide for Injection: 30 minutes after initiation of secretin infusion, administer Sincalide 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 Sincalide for Injection 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. Alternatively, Consider an 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.

2.2 Preparation Instructions

A subsection with step-by-step preparation instructions was created by the review team and reviewed by OPQ and the Division of Medication Errors Prevention and Analysis (complete instructions not shown here). DMEPA noted that the storage time for the post dilution intravenous infusion is very short and recommended increasing the prominence of this important information and to inform persons responsible for preparing the product and minimize the risk of administering expired products, as shown below:

For Intravenous Injection

- ...
- Store the Sincalide reconstituted solution at room temperature. *Discard after 8 hours*...

For Intravenous Infusion

- …
- Store the Sincalide diluted solution at room temperature. *Discard after 1 hour*...

3 DOSAGE FORMS AND STRENGTHS

The strength, identifying characteristics and limited packaging information were included as shown:

For Injection: 5 mcg of sincalide as a lyophilized white cake or powder for reconstitution in a single-dose vial

4 CONTRAINDICATIONS

As noted below, cases of serious hypersensitivity reactions were identified postmarketing for sincalide by the Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance-I (DPV-I). Therefore, reference to anaphylaxis and anaphylactic shock with cross-references to a newly created subsection of Warnings and Precautions and Adverse Reactions section were added:

Sincalide for Injection is contraindicated in patients with:

- a history of a hypersensitivity reaction to sincalide. Serious hypersensitivity reactions have included anaphylaxis and anaphylactic shock *[see Warnings and Precautions (5.1), Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis, Anaphylactic Shock and Other Hypersensitivity Reactions

As a result of a DPV-I postmarketing safety review of postmarketing spontaneous reports for sincalide reported to FAERS between July 21, 1976 and March 25, 2016 (NDA 17697 by Kimberly Swank, dated May 18, 2016 in DARRTS), a new subsection was added to reflect the risk of serious hypersensitivity reactions and a corresponding mitigation strategy. See additional discussion regarding the Adverse Reactions section, below.

In postmarketing experience, anaphylaxis, anaphylactic shock and other serious hypersensitivity reactions have been reported during and within one hour following administration of sincalide *[see Adverse Reactions (6)]*.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when Sincalide for Injection is administered. If anaphylaxis or other hypersensitivity reactions occur, immediately discontinue the infusion and initiate appropriate medical treatment. Observe patients closely during and after the infusion. Do not reinitiate Sincalide for Injection in patients who have experienced symptoms of hypersensitivity *[see Contraindications (4)]*.

5.2 Evacuation of Gallstones

Existing information was retained and statements that minimize the risk were deleted:

(b) (4) Stimulation of gallbladder contraction in patients with small gallbladder stones could lead to the evacuation of the stones from the gallbladder, resulting in their lodging in the cystic duct or in the common bile duct. (b) (4)

(b) (4)

5.3 Adverse Reactions with Intravenous Injection

This subsection was created using information found in the Dosage and Administration and Adverse Reactions sections. The applicant confirmed, using literature data, that the specific adverse reaction terms described here can be mitigated by a slower infusion rate.

Administration of Sincalide for Injection as an intravenous injection such as nausea, vomiting, abdominal pain or cramping, dizziness, and flushing *[see Adverse Reactions (6)]*. These reactions are generally transient. To reduce the risk of adverse reactions with intravenous injection when used to simulate contraction of the gallbladder or accelerate transit of a barium meal through the small intestine, administer Sincalide for Injection as an intravenous infusion over 50 or 30 minutes, respectively *[see Dosage and Administration (2.1)]*.

5.4 Preterm Labor or Spontaneous Abortion

A statement about the risk of spontaneous abortion or premature induction of labor is described in the Kinevac PI in the Warnings section. This statement is based upon a single a case report describing a case of threatened abortion.[4]

A literature search, conducted both by the applicant and by the Maternal Health team in the Division of Pediatrics and Maternal Health (DMPH), did not identify any studies or additional adverse effects of sincalide in pregnant humans. The applicant also conducted a review of FAERS from January 1976 through December 2013. No cases related to pregnancy, other than the previously mentioned case of threatened abortion, were identified.

The existing Warning was revised to acknowledge the limited information:

[4] Silberstein EB, Marcus CS. Unreported side effect of sincalide. Radiology. 1994;190:902.

(b) (4) 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)]*.

6 ADVERSE REACTIONS

The existing safety information was reorganized into common and less common adverse reactions reported either during clinical trials or postmarketing. The following additional less common adverse reactions reported postmarketing, identified in a 2016 DPV-I review as being associated with serious hypersensitivity reactions were added: *anaphylaxis, anaphylactic shock, throat tightness, bradycardia, hives, itching*. Other terms associated with vasovagal reactions in the DPV review were also added: *loss of consciousness, and syncope*

Seizures was also added. These reactions were considered by the clinical reviewer to be distinct from the hypersensitivity and vasovagal reactions described above and are biologically plausible due to the fact that CCK has been shown to enter the brain and cause seizures in animals.

Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency, reliably, or to establish a causal relationship to drug exposure.

The most frequent adverse reactions (20% or greater) are gastrointestinal: abdominal discomfort or pain, and nausea; these may not necessarily indicate an abnormality of the biliary tract unless there is other clinical or radiologic evidence of disease.

Less common adverse reactions include:
Hypersensitivity reactions: anaphylaxis and anaphylactic shock, hypotension, throat tightness, bradycardia, shortness of breath, nausea, abdominal cramping, diaphoresis, hives, rash, itching; and numbness of face, lips and eye *[see Contraindications (4)]*.

Neurological reactions: seizures, headache.

Vasovagal reactions: dizziness, loss of consciousness, nausea, diaphoresis, syncope and hypotension (generally self-limiting).

Other: nausea, vomiting, flushing, hypertension, urge to defecate, diarrhea, sneezing.

CDTL Comment: An email from DPV (Kimberly Swank) on January 16, 2018 stated: DPV performed an updated FAERS search for the period of March 26, 2016 (end date of FAERS search from 2016 DPV review) through January 15, 2018. All adverse events were with sincalide were reviewed and no additional cases of seizures were reported. Most cases reported the preferred term of "drug ineffective" or preferred terms associated with signs and symptoms of hypersensitivity reactions.

Therefore, no additional action is required at this time. DPV will continue to monitor for adverse events of seizure.

7 DRUG INTERACTIONS

7.1 Drugs that Affect Gallbladder Motility or Contractile Response

Since sincalide potentially interacts with other drugs and there is no Drug Interactions section, the applicant was asked to consider including a description of the pharmacodynamic interaction between sincalide and other drugs that may affect gallbladder contraction based upon up-to-date published literature.

The applicant acknowledged the request based upon consensus recommendation of an interdisciplinary panel of experts;[5] however, they noted that they were not able to find any specific studies or literature that provide supportive data for the recommendations therein, specifically for the time windows stated for separation between sincalide administration and administration of opiates and anticholinergics (48 hours). They also noted that although they identified additional literature citations describes medications that may influence gallbladder motility or contractile response, most were not specific to sincalide in terms of the ability to either inhibit or increase the desired pharmacodynamic response. Specific citations varied considerably in terms of which specific drugs are listed. The most inclusive review lists over a dozen drugs or classes of drugs that can stimulate or inhibit gallbladder motility[6] but other publications mention shorter lists of drugs and even combination of drugs.

The review team concluded that without specific studies or literature documentation, other than treatment guidelines, specific examples should not be included. However, a general statement and recommendations were added:

> 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.

8 USE IN SPECIFIC POPULATIONS

The Maternal Health team in DPMH and the Pharmacology/Toxicology reviewers revised subsections 8.1 Pregnancy and 8.2 Lactation to comply with the Pregnancy and Lactation Labeling Rule (PLLR), as described below. It was noted that no studies specific to the effects of sincalide on human fertility were reported by the applicant. One publication reported no adverse effect of cholecystokinin on mating behavior in male and female rats. Therefore, the Maternal Health team concluded no data are available on the effects of sincalide on human fertility or hormonal contraception and the limited data in animals do not indicate an adverse effect of sincalide on fertility. Therefore, subsection 8.3 Females and Males of Reproductive Potential was not included

8.1 Pregnancy

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. Reference is

[5] Dibaise JK, Richmond BK, Ziessman, HA, et. al. Cholecystokinin-cholescintigraphy in adults: consensus recommendations of an interdisciplinary panel. Clin Nucl Med 2012;37(1):63-70.
[6] Van Erpecum KJ, Venneman NG, Portincasa P, et al. Review article: agents affecting gall-bladder motility – role in treatment and prevention of gallstones. Aliment Pharmacol Ther 2000;14(Suppl 2):66-70.

made back to the Warnings and Precaution section regarding the risk of preterm labor or spontaneous abortion.

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 (5.4)]*. 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 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 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 to4% 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 to 13) 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 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

There are no data available from animal studies on the excretion of sincalide into milk. The applicant did not find any cases in FAERS related to lactation.

The amount of sincalide in breastmilk is likely to be low (due to the low molecular weight) and oral absorption is unlikely (destroyed in the infant's gastrointestinal tract). In addition, the adverse effects that occurred in neonatal rats were due to direct injection of sincalide to the neonatal rats and not due to expose of sincalide through milk.

Two publications were submitted by the applicant, and the Maternal Health team reviewed the LactMed database. They concluded that cholecystokinin is present in breast milk in low concentrations; 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. Therefore, there is no reason to recommend against breastfeeding.

Risk Summary
There are no data regarding 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 condition.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established. Nonclinical data regarding direct injection of sincalide in neonatal rats reduced milk consumption was moved into this section under the subheading of Animal 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 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).

8.5 Geriatric Use

This subsection was created, as required under the labeling regulations under 21 CFR 201.57.

Clinical studies of sincalide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

This section should be based upon human data and animal data not usually included, unless human data are not available. The following animal information was thought to be relevant to humans and retained in this section.

In the event of an overdose, symptoms related to vagal stimulation, such as gastrointestinal symptoms (abdominal cramps, nausea, vomiting and diarrhea), hypotension with dizziness or fainting may occur. Overdosage symptoms should be treated symptomatically and should be of short duration.
A single bolus intravenous injection of 0.05 mcg/kg (approximately 2 to 3 times the human dose of 0.02 mcg/kg), sincalide caused hypotension and bradycardia in dogs. In addition, higher doses injected intravenously once or repeatedly in dogs caused syncope and ECG changes (approximately 5 times the human dose of 0.02 mcg/kg). These effects were attributed to sincalide-induced vagal stimulation in that all were prevented by pretreatment with atropine or bilateral vagotomy.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Existing information was retained and revised for clarity:

When injected intravenously, Sincalide stimulates gallbladder contraction and reduction in size. The evacuation of bile that results is similar to that which occurs physiologically in response to endogenous cholecystokinin. Sincalide also stimulates pancreatic secretion and intestinal motility causing pyloric contraction and slows gastric emptying.

Concurrent administration of sincalide with secretin increases both the volume of pancreatic secretion and the output of bicarbonate and enzymes. This combined effect of secretin and sincalide permits the assessment of specific pancreatic function through measurement and analysis of the duodenal aspirate.

12.2 Pharmacodynamics

Existing information was rewritten to describe the pharmacodynamic effect expected with the recommended dosage of sincalide.

The applicant requested removal of the information regarding a fatty meal stating that since sincalide is efficient in producing gall bladder contraction within 5 to15 minutes, it is not helpful for physicians or patients to be told that an alternative approach such as ingesting a fatty meal takes much longer.

Following an (b) (4) intravenous (bolus) injection of 0.02 mcg/kg (b) (4) of sincalide, maximal (b) (4) contraction of the gallbladder (b) (4) occurred in 5 to 15 minutes, (b) (4) (b) (4) (b) (4) Sincalide reduced gallbladder contraction by at least 40%, which is generally considered satisfactory contraction.

12.3 Pharmacokinetics

No information on pharmacokinetics is included in the Kinevac PI. The review team asked the applicant to consider addition information on the half-life of sincalide, to support the pharmacodynamic information. The applicant noted that a half-life of 2.5 to 3 minutes referenced in the literature in 1975 was obtained following intravenous injection of a "natural porcine 33-amino acid form of CCK" and not CCK-8, which is sincalide.[7]

The Clinical Pharmacology review team concurred and noted that other literature references do not have a primary data source or cite the 1975 article. A publication from 2003 (2003) noted a half-life of 23 ± 16 min for CCK-8 in patients with sphincter of Oddi spasm.[8] The relevance of this information to the intended patient population is unclear. Finally, the half-life of endogenous human CCK (a mixture of CCK-58, 33, 22, and 8) is suggested to be around 5 to 7 minutes, but no source data are cited.[9] Therefore, subsection 12.3 will not be included as no reliable data are available to support the half-life of CCK-8.

[7] Thompson JC, Fender HR, Ramus NI, et al. Cholecystokinin metabolism in man and dogs. Ann Surg 1975 Oct;182(4):496-504.
[8] Krishnamurthy S, Cerulli-Switzer J, Champman N, et al. Comparison of gallbladder function obtained with regular CCK-8 and pharmacy-compounded CCK-8. J Nucl Med 2003;44(4):499-504.
[9] Harvey RF, Dowsett L, Hartog M, et al. A radioimmunoassay for cholecystokinin-pacreozymin. Lancet 1973:2:826-8.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The following statement regarding animal studies was retained in labeling, despite the lack of data. Since preterm labor or spontaneous abortion are potential adverse outcomes in humans, it may be informative to prescribers to know that animal data on fertility and early embryonic development are lacking.

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

17 PATIENT COUNSELING INFORMATION

This section was created, as required to describe risk information the healthcare provider should convey to the patient.

> Anaphylaxis, Anaphylactic Shock and Other Hypersensitivity Reactions
> Inform patients that hypersensitivity reactions, including anaphylaxis and anaphylactic shock have been reported during or following administration of Sincalide for Injection. Advise patients to report immediately to a healthcare provider if they experience symptoms of a hypersensitivity reaction *[see Warnings and Precautions (5.1)]*.
>
> Gastrointestinal Adverse Reactions
> Advise patients that Sincalide for Injection may cause transient gastrointestinal symptoms *[see Warnings and Precautions (5.3)]*.
>
> Pregnancy
> Advise pregnant women of the potential risk for preterm labor and spontaneous abortion *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

OTHER LABELING
Carton/Container Labeling

OPQ/DMEPA: Revised labeling submitted February 12, 2018 is acceptable.

13. Risk Evaluation and Mitigation Strategy, Postmarketing Commitments, Postmarketing Requirements

A Risk Evaluation and Management Strategy (REMS) is not required for this application.

There are no postmarketing requirements (PMRs).

The following are postmarketing commitments (PMCs) proposed by OPQ and accepted by the applicant. Because this is a tentative review, these PMCs will be requested if/when the application is fully approved.

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

2. 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.

14. Recommended Comments to the Applicant

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOETTE M MEYER
02/23/2018
CDTL

JOYCE A KORVICK
02/23/2018