CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

017697Orig1s031

Trade Name:	Kinevac
Generic or Proper Name:	Sincalide for Injection
Sponsor:	Bracco Diagnostics Inc.
Approval Date:	February 9, 2018
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.

CENTER FOR DRUG EVALUATION AND RESEARCH

017697Orig1s031

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology / Virology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

017697Orig1s031

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 017697/S-031

SUPPLEMENT APPROVAL

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Affairs
259 Prospect Plains Road, Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on February 1, 2018 (eCTD SN0015) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for KINEVAC® (Sincalide for Injection), 5 mcg/vial.

This "Changes Being Effected" (CBE) supplemental new drug application proposes the removal of the intramuscular (IM) dose information from the Dosage and Administration section of the prescribing information (PI).

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the following minor editorial revision: the revision date for the PI has been changed from 'January 2018' to 'February 2018'.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending CBE supplements, as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the Guidance for Industry titled "SPL Standard for Content of Labeling Technical Qs & As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft (MS) Word format that includes the changes (along with the minor editorial revision noted above) approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean MS Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Benjamin Vali, Regulatory Project Manager, at (301) 796-4261 or benjamin.vali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

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

/s/

JOYCE A KORVICK
02/09/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

017697Orig1s031

LABELING

KINEVAC- sincalide injection, powder, lyophilized, for solution
Bracco Diagnostics Inc.

KINEVAC®
Sincalide for Injection

DESCRIPTION

Kinevac (Sincalide for Injection) is a cholecystopancreatic-gastrointestinal hormone peptide for parenteral administration. The agent is a synthetically-prepared C-terminal octapeptide of cholecystokinin. Each vial of sincalide provides a sterile nonpyrogenic lyophillized white powder consisting of 5 mcg sincalide with 170 mg mannitol, 30 mg arginine hydrochloride, 15 mg lysine hydrochloride, 9 mg potassium phosphate dibasic, 4 mg methionine, 2 mg pentetic acid, 0.04 mg sodium metabisulfite, and 0.005 mcg polysorbate 20. The pH is adjusted to 6.0 - 8.0 with hydrochloric acid and/or sodium hydroxide prior to lyophilization. Sincalide is designated chemically as L-α-aspartyl-O-sulfo-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl- L-α-aspartyl-L-phenylalaninamide. Graphic formula:

$C_{49}H_{62}N_{10}O_{16}S_3$ MW 1143.27 CAS-25126-32-3

CLINICAL PHARMACOLOGY

When injected intravenously, sincalide produces a substantial reduction in gallbladder size by causing this organ to contract. The evacuation of bile that results is similar to that which occurs physiologically in response to endogenous cholecystokinin. The intravenous (bolus) administration of sincalide causes a prompt contraction of the gallbladder that becomes maximal in 5 to 15 minutes, as compared with the stimulus of a fatty meal which causes a progressive contraction that becomes maximal after approximately 40 minutes. Generally, a 40 percent reduction in radiographic area of the gallbladder is considered satisfactory contraction, although some patients will show area reduction of 60 to 70 percent.

Like cholecystokinin, sincalide stimulates pancreatic secretion; concurrent administration with secretin increases both the volume of pancreatic secretion and the out-put of bicarbonate and protein (enzymes) by the gland. This combined effect of secretin and sincalide permits the assessment of specific pancreatic function through measurement and analysis of the duodenal aspirate. The parameters usually determined are: volume of the secretion; bicarbonate concentration; and amylase content (which parallels the content of trypsin and total protein).

Both cholecystokinin and sincalide stimulate intestinal motility, and may cause pyloric contraction which retards gastric emptying.

INDICATIONS AND USAGE

Kinevac (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.

CONTRAINDICATIONS

The preparation is contraindicated in patients hypersensitive to sincalide and in patients with intestinal obstruction.

WARNINGS

Because of Kinevac's effect on smooth muscle, pregnant patients should be advised that spontaneous abortion or premature induction of labor may occur (see Pregnancy Category B).

PRECAUTIONS

General

The possibility exists that 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. The risk of such an event is considered to be minimal because sincalide, when given as directed, does not ordinarily cause complete contraction of the gallbladder.

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.

Teratogenic Effects

Pregnancy Category B

Reproduction studies in rats in which sincalide was administered subcutaneously at doses up to 12.5 times the maximum recommended human dose revealed no evidence of harm to the fetus due to sincalide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed (see WARNINGS).

Labor and Delivery

Sincalide should not be administered to pregnant women near term because of its effect on smooth muscle; the possibility of inducing labor prematurely exists. The effects of sincalide on labor, delivery and lactation in animals has not been determined (see WARNINGS).

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sincalide is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Reactions to sincalide are generally mild and of short duration. The most frequent adverse reactions were abdominal discomfort or pain, and nausea; rapid intravenous injection of 0.04 mcg sincalide per kg expectably causes transient abdominal cramping. These phenomena are usually manifestations of the physiologic action of the drug, including delayed gastric emptying and increased intestinal motility. These reactions occurred in approximately 20 percent of patients; they are not to be construed as necessarily indicating an abnormality of the billiary tract unless there is other clinical or radiologic evidence of disease.

The incidence of other adverse reactions, including vomiting, flushing, sweating, rash, hypotension, hypertension, shortness of breath, urge to defecate, headache, diarrhea, sneezing, and numbness was less than 1 percent; dizziness was reported in approximately 2 percent of patients. These manifestations are usually lessened by slower injection rate.

OVERDOSAGE

Although no overdosage reports have been received, gastrointestinal symptoms (abdominal cramps, nausea, vomiting and diarrhea) would be expected. Hypotension with dizziness or fainting might also occur. Overdosage symptoms should be treated symptomatically and should be of short duration. Starting with single bolus i.v. injection comparable to the human does of 0.4 mg/kg, sincalide caused hypotension and bradycardia in dogs. Higher doses injected once or repeatedly in dogs caused syncope and ECG changes in addition. These effects were attributed to sincalide-induced vagal stimulation in that all were prevented by pretreatment with atropine or bilateral vagotomy.

DOSAGE AND ADMINISTRATION

Reconstitution and Storage

Sincalide for Injection may be stored at room temperature prior to reconstitution.

To reconstitute, aseptically add 5 mL of Sterile Water for Injection USP to the vial. This solution may be kept at room temperature and should be used within 8 hours of reconstitution, after which time any unused portion should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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 (see ADVERSE REACTIONS), 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. When Kinevac (Sincalide for Injection) is used in cholecystography, roentgenograms are usually taken at five-minute intervals after the injection. For visualization of the cystic duct, it may be necessary to take roentgenograms at one-minute intervals during the first five minutes after the injection.

For the Secretin-Kinevac 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 Kinevac 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 Kinevac 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 Kinevac after the barium meal is beyond the proximal jejunum. (Sincalide, like cholecystokinin, may cause pyloric contraction.) 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.

Sodium Chloride Injection dilutions may be kept at room temperature and should be used within one hour of dilution.

HOW SUPPLIED

Kinevac (Sincalide for Injection) is supplied in packages of 10 vials containing 5 mcg of sincalide per vial (NDC 0270-0556-15).

Storage

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

U.S. Patent 6,803,046

Manufactured for
Bracco Diagnostics Inc.
Monroe Township, NJ 08831
by Jubilant HollisterStier LLC
Spokane, WA 99207

Printed in USA
Revised February 2018
875016-H05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

017697Orig1s031

OTHER REVIEW(S)

Division of Gastroenterology and Inborn Errors Products (DGIEP)

REGULATORY PROJECT MANAGER LABELING REVIEW

NDA Application: 017697/"Changes Being Effected" (CBE) Supplement-031 (S-031)

Name of Drug: KINEVAC (sincalide for injection), 5 mcg/vial

Applicant: Bracco Diagnostics Inc.

Labeling Reviewed

Submission Date: February 1, 2018

Receipt Date: February 1, 2018 (SDN 217; eCTD SN0015)

Background and Summary Description: On August 31, 2017, Bracco Diagnostics Inc. (hereafter, 'Bracco') submitted their 45th annual report for KINEVAC (SDN 206; eCTD SN0005), which was originally approved on July 21, 1976. The FDA review team discovered a statement in the Dosage and Administration section of the prescribing information (PI; non-Physician Labeling Rule [PLR] format) pertaining to an intramuscular route of administration in the Dosage and Administration section, which was not known to be an approved route of administration for this drug product. Consequently, on January 8, 2018, an information request (IR) was sent to Bracco by FDA (Reference ID: 4204706) for clarification purposes. The content of the IR (in *italics* below) is as follows:

There is a sentence under the "Dosage and Administration" section within the most recent prescribing information (PI) dated July 2014 that was submitted in the latest annual report, which states:

"…alternatively, an intramuscular dose of 0.1 mcg/kg may be given."

It is not clear when this information was added to the PI. We have reviewed the FDA's records pertaining to the intramuscular (IM) route of administration from 1976 to 1996 and have not found any documentation as to when and how this route of administration was approved. We therefore request that you provide responses to the following two queries:

1. *Provide the date and a summary of the data supporting the approval of the IM route of administration.*

2. *KINEVAC underwent a reformulation in 2002, as reflected by the approval of Supplement-013 on November 27, 2002. If the IM route of administration was approved prior to 2002, provide a summary of the data that supported the continued approval of the IM route of administration for the reformulated product.*

Bracco's response to this IR was received on January 16, 2018 (SDN 214; eCTD SN0012). Their response (in *italics* below) is summarized as follows:

Bracco has reviewed the historical files related to Kinevac labeling and has discovered the following:

- *On March 4, 1987 Squibb (NDA sponsor at that time – ownership of this NDA was transferred to Bracco from Squibb (actually Bristol-Myers Squibb at the time) in August 1994) submitted a Content and Format labeling submission as required per CFR regulations in which the statement in question was added.*
- *On May 29, 1987, FDA made a verbal request to Squibb to annotate the proposed changes.*
- *On June 12, 1987, Squibb responded to FDAs request for annotation, but withdrew the proposed revision regarding the addition of this statement ["…alternatively, an intramuscular dose of 0.1 mcg/kg may be given."].*
- *The March 1988 printing of the Prescribing Information [J3-398E] inadvertently included the withdrawn statement and has been carried forward since.*

In response to FDAs questions, no data was ever submitted in support of this route of administration; nor was it part of the reformulation efforts of 2002. The labeling will be revised to remove this statement and a Changes Being Effected (CBE) labeling supplement will be submitted shortly.

On February 1, 2018, Bracco submitted the aforementioned CBE labeling supplement (SDN 217; eCTD SN0015), and this labeling supplement (i.e., S-031) is the subject of this labeling review.

Review

The statement "…alternatively, an intramuscular dose of 0.1 mcg/kg may be given" has been removed from the Dosage and Administration section and the revision date (i.e., month/year) updated to 'January 2018' by the Sponsor. The RPM contacted Bracco to state that the Agency will revise this date to 'February 2018' in order to reflect the correct month and year of submission. This minor edit would also be noted in the body of the action letter. Bracco concurred with this approach (see attached email).

Recommendations

From a regulatory and labeling standpoint, this supplement is recommended for approval. The aforementioned minor edit will be made to the PI and will also be noted in the body of the approval letter.

Benjamin Vali, M.S.	February 7, 2018
Regulatory Project Manager	Date
Joette Meyer, Pharm.D.	February 7, 2018
Associate Director for Labeling	Date

Vali, Benjamin P

From: Benson Melanie <Melanie.Benson@diag.bracco.com>
Sent: Tuesday, February 06, 2018 8:10 AM
To: Vali, Benjamin P
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Ben,

Thank you for your note. Bracco does agree with your approach – we had hoped to submit the CBE-0 supplement at the end of January but did not get the SPL in time to do so, and I did not want to send back to the vendor and delay a few more days. We will make sure that the production labels have a February 2018 date. Will this be acceptable or should we just leave it this one time and be more cautious in the future?

Thank you in advance.
Best regards, Melanie Benson
Bracco Diagnostics Inc
609-514-2254

From: Vali, Benjamin P [mailto:benjamin.vali@fda.hhs.gov]
Sent: Monday, February 05, 2018 4:51 PM
To: Benson Melanie <Melanie.Benson@diag.bracco.com>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Melanie,

Here is the acknowledgement letter for the CBE supplement.

Just one note with respect to the content of labeling (i.e., the PI) that was submitted. The revision date in the submission showed 'January 2018'. The revision date should correspond to the Month/Year of action. Since we will take action on this supplement this upcoming week, we will simply change 'January 2018' to 'February 2018' (and, of course, leave everything else alone/as is). This minor editorial revision will be noted in the action letter. I just wanted to give you the heads up on that. No need for you to resubmit anything.

Please confirm whether you agree with this approach, and thanks again!

Best,
Ben

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Thursday, February 01, 2018 3:02 PM
To: Vali, Benjamin P <benjamin.vali@fda.hhs.gov>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Good Afternoon Ben,

Surprise! Bracco submitted the CBE-0 labeling supplement for Kinevac about 30 minutes ago. The SPL was submitted through the gateway and passed validation, so I would imagine the new PI should be posted on DailyMed within the next day or two. Enjoy!

Best regards, Melanie Benson

From: Vali, Benjamin P [mailto:benjamin.vali@fda.hhs.gov]
Sent: Tuesday, January 30, 2018 8:39 AM
To: Benson Melanie <Melanie.Benson@diag.bracco.com>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Melanie,

Thanks for the update. Sounds good. I will look out for it.

Best,
Ben

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Tuesday, January 30, 2018 8:04 AM
To: Vali, Benjamin P <benjamin.vali@fda.hhs.gov>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Good Morning Ben,

Yes, we are hoping to submit it this week. We are waiting for the SPL conversion.
I will let you know once it is submitted.

Best regards, Melanie

From: Vali, Benjamin P [mailto:benjamin.vali@fda.hhs.gov]
Sent: Monday, January 29, 2018 3:13 PM
To: Benson Melanie <Melanie.Benson@diag.bracco.com>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Melanie,

As per our phone discussion last week, will be CBE be submitted this week? Please let me know.

Thanks,
Ben

From: Vali, Benjamin P
Sent: Wednesday, January 24, 2018 9:46 AM
To: 'Benson Melanie' <Melanie.Benson@diag.bracco.com>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Melanie,

Just following up. Thanks, and I hope all is well with you.

Best,
Ben

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Thursday, January 18, 2018 11:55 AM
To: Vali, Benjamin P <benjamin.vali@fda.hhs.gov>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Ben,

I apologize for the delay. I just checked again with my labeling person and we will be able to provide you with an answer either tomorrow or Monday. We need to work with the CMO, Jubilant HollisterStier, on this as they do the actual labeling.

Best regards, Melanie Benson

From: Vali, Benjamin P [mailto:benjamin.vali@fda.hhs.gov]
Sent: Thursday, January 18, 2018 10:57 AM
To: Benson Melanie <Melanie.Benson@diag.bracco.com>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Melanie,

Just following up. Thanks, and hope all is well.

Best,
Ben

From: Vali, Benjamin P
Sent: Tuesday, January 16, 2018 11:33 AM
To: Benson Melanie <Melanie.Benson@diag.bracco.com>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Thanks Melanie. I did have one follow-up question upon review of your submitted response. In your response, you note that a Changes Being Effected (CBE-) labeling supplement will be submitted shortly. When can we expect this submission?
Thanks, as always,
Ben

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Tuesday, January 16, 2018 7:35 AM
To: Vali, Benjamin P <benjamin.vali@fda.hhs.gov>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Ben,

Thank you. And if you have any further questions, please contact me.

Best regards, Melanie Benson

From: Vali, Benjamin P [mailto:benjamin.vali@fda.hhs.gov]
Sent: Monday, January 15, 2018 5:50 PM
To: Benson Melanie <Melanie.Benson@diag.bracco.com>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Hi Melanie,

I just wanted to let you know that we received your formal response to the NDA through the Gateway earlier this afternoon.

Thanks again,
Ben

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Tuesday, January 09, 2018 12:11 PM
To: Vali, Benjamin P <benjamin.vali@fda.hhs.gov>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Thank you Ben.

From: Vali, Benjamin P [mailto:benjamin.vali@fda.hhs.gov]
Sent: Tuesday, January 09, 2018 12:10 PM
To: Benson Melanie <Melanie.Benson@diag.bracco.com>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Dear Melanie,

Thanks for your email.

To answer your question, this pertained to our review of your annual report submitted last August. The Agency reviews annual reports (under INDs, NDAs, and BLAs), but they tend to fall on the backburner due to all other competing work (e.g., new IND reviews, sponsor meetings, etc.). Upon review (albeit late), the clinical team wanted to inquire about the IM route. Hope this answers your question, and thanks again.

Best,
Ben

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Tuesday, January 09, 2018 10:26 AM
To: Vali, Benjamin P <benjamin.vali@fda.hhs.gov>
Subject: RE: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Good Morning Mr Vali,

Bracco Diagnostics Acknowledges this request and will respond accordingly.
If I may, can I ask how this was discovered?

Best regards,
Melanie Benson
Bracco Diagnostics Inc
609-514-2254

From: Vali, Benjamin P [mailto:benjamin.vali@fda.hhs.gov]
Sent: Monday, January 08, 2018 5:03 PM
To: Benson Melanie <Melanie.Benson@diag.bracco.com>
Subject: NDA 017697 – KINEVAC (sincalide for Injection): Request for Information

Dear Ms. Benson,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for KINEVAC (sincalide for injection). We are conducting a review of your latest annual report submitted and received on August 31, 2017 (eCTD SN0005), and we have the following request for information.

Please formally submit your written response to the NDA by close-of-business (COB) Monday January 15, 2018. Please also provide an electronic (via email) true-and-exact courtesy copy of this formal response to me.

Labeling

There is a sentence under the "Dosage and Administration" section within the most recent prescribing information (PI) dated July 2014 that was submitted in the latest annual report, which states:

"…alternatively, an intramuscular dose of 0.1 mcg/kg may be given."

It is not clear when this information was added to the PI. We have reviewed the FDA's records pertaining to the intramuscular (IM) route of administration from 1976 to 1996 and have not found any documentation as to when and how this route of administration was approved. We therefore request that you provide responses to the following two queries:

1. Provide the date and a summary of the data supporting the approval of the IM route of administration.

2. KINEVAC underwent a reformulation in 2002, as reflected by the approval of Supplement-013 on November 27, 2002. If the IM route of administration was approved prior to 2002, provide a summary of the data that supported the continued approval of the IM route of administration for the reformulated product.

Please confirm receipt, and do let me know if you have any questions.

Kind regards,
Ben

Benjamin Vali, MS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
10903 New Hampshire Ave., WO22-RM5245
Silver Spring, MD 20903
Phone: 301-796-4261
Fax: 301-796-9904

Le informazioni contenute in questo messaggio di posta elettronica e relativi allegati sono riservate e confidenziali e ne è vietata la diffusione in qualunque modo eseguita. Qualora Lei non fosse la persona a cui il presente messaggio è destinato, La invitiamo ad eliminarlo e a darcene gentile comunicazione.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

Le informazioni contenute in questo messaggio di posta elettronica e relativi allegati sono riservate e confidenziali e ne è vietata la diffusione in qualunque modo eseguita. Qualora Lei non fosse la persona a cui il presente messaggio è destinato, La invitiamo ad eliminarlo e a darcene gentile comunicazione.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

Le informazioni contenute in questo messaggio di posta elettronica e relativi allegati sono riservate e confidenziali e ne è vietata la diffusione in qualunque modo eseguita. Qualora Lei non fosse la persona a cui il presente messaggio è destinato, La invitiamo ad eliminarlo e a darcene gentile comunicazione.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

Le informazioni contenute in questo messaggio di posta elettronica e relativi allegati sono riservate e confidenziali e ne è vietata la diffusione in qualunque modo eseguita. Qualora Lei non fosse la persona a cui il presente messaggio è destinato, La invitiamo ad eliminarlo e a darcene gentile comunicazione.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

Le informazioni contenute in questo messaggio di posta elettronica e relativi allegati sono riservate e confidenziali e ne è vietata la diffusione in qualunque modo eseguita. Qualora Lei non fosse la persona a cui il presente messaggio è destinato, La invitiamo ad eliminarlo e a darcene gentile comunicazione.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

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

/s/

BENJAMIN P VALI
02/07/2018

JOETTE M MEYER
02/07/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

017697Orig1s031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 017697/S-031

CBE SUPPLEMENT – ACKNOWLEDGEMENT

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Affairs
259 Prospect Plains Road, Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA NUMBER: 017697

SUPPLEMENT NUMBER: 031

PRODUCT NAME: KINEVAC (sincalide) Injectable, 5 mcg/vial

DATE OF SUBMISSION: February 1, 2018

DATE OF RECEIPT: February 1, 2018 (eCTD SN0015)

This supplemental application, submitted as a "Changes Being Effected" (CBE) supplement, proposes the following change(s): removal of the intramuscular dose information from the Dosage and Administration section of the prescribing information (PI).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 2, 2018 in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be August 1, 2018.

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format to the FDA automated drug registration and listing system (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that includes the proposed labeling changes with the addition of any labeling changes in pending

previously submitted CBE supplements. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, contact me at (301) 796-4261 or benjamin.vali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Benjamin Vali, M.S.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

BENJAMIN P VALI
02/05/2018