PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

SINCALIDE FOR INJECTION

Sincalide for Injection

Powder for Solution, 5 mcg / vial, Intravenous

House Std.

Diagnostic Cholecystokinetic

AVIR Pharma Inc.
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Blainville, Quebec
J7C 3V4
www.avirpharma.com

Date of Initial Authorization:
November 22, 2019

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October 20, 2022

Submission Control Number: 264855

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, General	10/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SINCALIDE FOR INJECTION (sincalide) is indicated for:

- Inducing contraction of the gallbladder during cholecystography. In many instances, the cystic and common bile ducts can also be visualized, especially if viewed 1 to 3 minutes after injection of sincalide. Contraction of the gallbladder provides bile that may be aspirated from the duodenum for diagnostic purposes, e.g., to determine the degree of cholesterol saturation.
- In conjunction with Secretin (Secretin-sincalide test) to stimulate pancreatic secretion for analysis of its composition and for cytological examination, e.g., in suspected cancer of the pancreas.
- The relief of postoperative ileus uncomplicated by inflammatory processes such as pancreatitis and peritonitis or by the presence of tumors or other obstructions in the lower digestive tract.
- Decreasing the small bowel transit time of contrast media.

1.1 Pediatrics

Pediatrics (<18 years): The safety and efficacy of sincalide in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): Clinical studies of sincalide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

2 CONTRAINDICATIONS

- SINCALIDE FOR INJECTION is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (see 7 WARNINGS AND PRECAUTIONS). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- SINCALIDE FOR INJECTION should not be used in cases where a fatty meal would be contraindicated such as: acute pancreatitis, acute cholecystitis, cystic duct obstruction, obstruction of the common bile duct, infection or empyema of the gallbladder, in patients with small gallbladder stones, appendicitis, hollow viscous perforation, peritonitis, penetrating, perforating or bleeding peptic ulcer, pyloric stenosis, mechanical obstruction of the gastrointestinal tract and generally, acute abdomen.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

For prompt contraction of the gallbladder during cholecystography, 0.02 mcg/kg (0.02 mL/kg); for a 50 kg patient, 1.0 mcg (1.0 mL) of sincalide 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/kg (2.0 mcg for a 50 kg patient) may be administered. Radiographs are usually taken at 5 minute intervals after the injection. For visualization of the cystic duct, it may be necessary to take radiographs at 1 minute intervals during the first 5 minutes after the injection.

For the Secretin-sincalide test of pancreatic function, the patient receives a dose of 0.25 units of secretin/kg infused intravenously over a 60 minute period. Thirty minutes after initiation of the secretin infusion, a separate intravenous infusion of SINCALIDE FOR INJECTION at a total dose of 0.02 mcg/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 FOR INJECTION solution to 30 mL with Sodium Chloride Injection USP and administer at a rate of 1 mL/minute.

For the resolution of postoperative ileus or to decrease small bowel transit time during roentgenologic examinations, a dose of 0.04 mcg sincalide/kg (2.8 mcg/70 kg) is injected intravenously over a 30 to 60 second interval. If a satisfactory response does not occur in patients with ileus, the same dose may be repeated or an increased dose of 0.08 mcg/kg given at 4 hour intervals up to a maximum of 5 doses of sincalide. The initial dose may be repeated once in patients undergoing radiologic study of the small bowel.

4.3 Reconstitution

Table 1 - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
5 mcg	5 mL of Sterile Water for Injection USP	5 mL	1.0 mcg/mL

After reconstitution, the solution may be stored at room temperature for up to 8 hours or under refrigeration for up to 24 hours after which time any unused portion should be discarded.

This reconstituted solution is used for contraction of the gallbladder during cholecystography but must be further diluted for the Secretin-sincalide test. For preparation instructions for intravenous infusion for test of pancreatic function see 4.2 Recommended Dose and Dosage Adjustment.

5 OVERDOSAGE

The symptoms of overdosage are likely to be mild and transitory gastrointestinal phenomena, consisting of abdominal discomfort, cramps, nausea, vomiting, and diarrhea. Dizziness and flushing may also occur.

Overdosage symptoms should be treated symptomatically and should be of short duration.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Sterile nonpyrogenic lyophilized white powder for solution for Injection 5 mcg / vial (1 mcg/mL after reconstitution)	Arginine hydrochloride, hydrochloric acid (and/or sodium hydroxide), lysine monohydrochloride, mannitol, methionine, pentetic acid, sodium metabisulfite

SINCALIDE FOR INJECTION is supplied in boxes of 10 vials.

7 WARNINGS AND PRECAUTIONS

General

In postmarketing experience, anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have been reported during and within one hour following administration of sincalide. 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 infusion. Do not reinitiate SINCALIDE FOR INJECTION in patients who have experienced symptoms of hypersensitivity (see 2 CONTRAINDICATIONS).

Gastrointestinal

SINCALIDE FOR INJECTION should be used with caution in patients with suspected duodenal, gastric or pyloric ulcer; gastrointestinal bleeding or ulceration of the bowel.

Because of the effects of SINCALIDE FOR INJECTION on the gastrointestinal system, the following should be borne in mind when SINCALIDE FOR INJECTION is administered:

- When a concurrent upper gastrointestinal series is planned, consider the effect of transient delayed gastric emptying produced by sincalide administration.
- The possibility of transient induced esophageal reflux due to the decrease in tone of the lower esophageal sphincter produced by sincalide.
- Due to increased bowel motility it may be difficult to perform a barium enema examination.
- Due to the stimulation of gallbladder contraction, there is the possibility of evacuation of small gallbladder stones, resulting in their lodging in the cystic or common bile ducts. This risk is considered minimal because sincalide, when given as directed, does not ordinarily cause complete contraction of the gallbladder.

Sensitivity/Resistance

Although sensitization to sincalide has not been reported, this possibility should be borne in mind, especially in patients who have previously received the drug.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of sincalide for use in pregnant women has not been established. Because of SINCALIDE FOR INJECTION's effect on smooth muscle, pregnant patients should be advised that spontaneous abortion or premature induction of labor may occur.

7.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

7.1.3 Pediatrics

Pediatrics <18 years: The safety and efficacy of sincalide in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects are often seen with sincalide; but they are limited mainly to mild and transitory gastrointestinal phenomena, usually consisting of abdominal discomfort, cramps and nausea. Dizziness, flushing, vomiting, sweating and an urge to defecate have occurred occasionally. Diarrhea, headache, bitter taste, shortness of breath, pain at the injection site, extremity tremor and sneezing have occurred rarely.

These phenomena may be manifestations of sincalide's physiological action, which include delayed gastric emptying and an increase in gastrointestinal motility.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drug interaction studies have not been conducted with sincalide. 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 stimulate contraction of the gallbladder.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sincalide is the synthetic octapeptide corresponding to the C-terminal octapeptide of the naturally- occurring hormone, cholecystokinin (CCK).

When injected intravenously, sincalide produces a rapid and pronounced 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.

10.2 Pharmacodynamics

Maximum contraction of the gallbladder occurs 5 to 15 minutes after injection of sincalide. Compared with a stimulus of a fatty meal, which causes a progressive contraction of the gallbladder that becomes maximal after approximately 40 minutes, the intravenous (bolus) injection of sincalide causes a prompt contraction of the gallbladder that is limited in duration.

Sincalide, like cholecystokinin, has been used in conjunction with secretin (Secretin-sincalide test) to stimulate pancreatic secretory function. This combined effect of secretin and sincalide permits the assessment of specific pancreatic function through measurement and the 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). This procedure may assist in the diagnosis of abnormal pancreatic function.

Both sincalide and cholecystokinin stimulate intestinal motility. The administration of sincalide to patients with postoperative ileus frequently leads to a restoration of normal bowel activity with a resultant increase in active bowel sounds and the occurrence of flatus and stools.

Sincalide also hastens the passage of radiopaque medium such as barium sulfate through the small bowel, thereby lessening the time and extent of radiation associated with fluroscopy and x-ray examination of the intestines. Since cholecystokinin has been shown to cause pyloric contraction, the barium meal must be beyond the pylorus for sincalide to have any effect. Both patient position and the quantity of barium in the small intestine have important effects on the transit time.

Human Studies:

Initial studies in normal volunteers established an intravenous (bolus) dose of 20 ng/kg as the optimal dose for producing contraction of the gallbladder. Studies of cholecystokinesis in 165 patients requiring cholecystography showed that this dose produced maximal contraction of the gallbladder in 52% of the patients while an additional injection of 40 ng/kg caused a maximal effect in a further 42%. Thirty-six percent of the patients experienced side-effects, mainly limited to mild and transient gastrointestinal phenomena (e.g. abdominal discomfort, nausea). Three instances of dizziness and 2 of flushing and 1 of an urge to defecate were reported. A similar study in a further 40 patients produced maximal gallbladder contraction at 20 ng/kg in 60% of the patients and at 40 ng/kg in the remainder. Eighteen patients experienced short periods of abdominal discomfort and 19 had transient nausea. Nine patients had both symptoms. No treatment was required for any of the adverse effects seen.

Studies of pancreatic secretion showed that sincalide, like cholecystokinin, stimulates pancreatic secretion. In general, an increased dose produced an increased volume of pancreatic secretion, with elevations in both bicarbonate and protein content. The effect of secretin was potentiated by sincalide, with the exception of the highest dose of sincalide tested (400 ng/kg per hour).

Lower oesophageal pressure was reduced in 7 normal male subjects by intravenous doses of sincalide ranging from 2.5 to 40 ng/kg. The calculated maximal decrease in pressure of the sphincter produced by sincalide was -8.82 mmHg, corresponding to a 60% decrease in the basal pressure.

The transit time of a barium mass moving through the small intestine was studied in 477 patients administered either sincalide or saline. Transit time averaged 47 and 34 minutes following administration of single doses of 20 ng/kg (111 patients) and 40 ng/kg (132 patients) of sincalide respectively, compared with 76 (109 patients) and >70 minutes (125 patients) after administration of similar doses of saline.

Clinical laboratory investigations conducted during these studies showed no evidence of disturbance in the renal, hepatic or hematopoietic systems.

11 STORAGE, STABILITY AND DISPOSAL

Store vials of lyophilized SINCALIDE FOR INJECTION at room temperature (15° - 30°C).

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

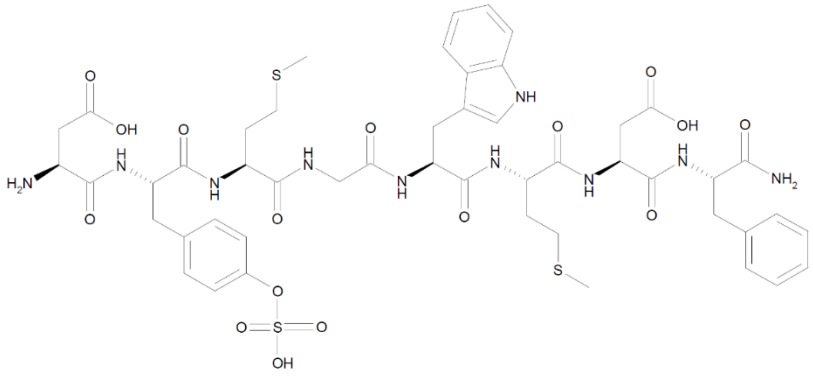
Drug Substance

Proper name: sincalide

Chemical name: L-α-aspartyl-O-sulfo-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-α-aspartyl-L-phenylalaninamide.

Molecular formula and molecular mass: $C_{49}H_{62}N_{10}O_{16}S_3$ 1143.27 g/mol

Structural formula:



Physicochemical properties: Sincalide is a white to off-white, fluffy powder.

14 CLINICAL TRIALS

Please refer to 10 CLINICAL PHARMACOLOGY.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute:

Intravenous doses of up to 20 mg/kg of sincalide administered to mice produced no signs of toxicity during a 5-day observation period.

LD50's obtained with sodium ipodate (Oragrafin®), administered to mice with or without 100 mcg sincalide, (10 mL/kg) were not significantly different.

Subacute:

Daily intravenous doses of 0.5, 1.5 or 5 mcg/kg of sincalide for a total of 14 doses (6 doses per week) given to groups of 10 mice, did not produce any gross toxicological changes. Four of the mice in the highest dose group showed slight-to-moderate elevations in hemoglobin. A fourth group of mice was given 5 mcg/kg of sincalide and 600 mg/kg of sodium ipodate and showed a slight decrease in body weight associated with decreased efficiency in food utilization.

Groups of beagle dogs were given intravenous doses of 20, 60 or 200 ng/kg of sincalide for 3 days and then 100, 300 and 1000 ng/kg 6 days per week for the remainder of a 3-week study. Another group was orally administered 3 g of sodium ipodate daily, followed 5 hours later by 300 ng/kg of sincalide intravenous for the duration of the study. No significant toxic signs attributable to the repeated administration of sincalide were seen. Transient bradycardia and syncope (often associated with injection times of less than 30 seconds) were seen in dogs given the highest dose of sincalide. Electro- cardiograms taken on the fifth and sixth dose days showed some changes in three dogs (1 maximal dose, 2 minimal doses). The ECG changes were characterized by T-wave reversal and change in amplitude, prolongation of the Q-T interval and elevation of the S-T segment were observed within 2 - 10 minutes after injection. Gross and microscopic post-mortem examinations revealed no changes attributable to sincalide, either alone or in combination with sodium ipodate.

Reproductive and Developmental Toxicology:

Teratology:

Sincalide was administered to rabbits, hamsters and rats, early in their respective gestation periods, at doses from 150 to 975 ng/kg per day. No teratological effects directly related to the administration of sincalide were seen in the offspring.

Pharmacodynamics:

Sincalide has been tested for gallbladder contracting activity in anesthetized guinea pigs and in anesthetized and unanesthetized dogs and proven effective with all types of gallbladder preparations.

In anesthetized cats, both sincalide and CCK reduce the flow resistance of the choledochoduodenal junction.

Sincalide produces an increase in the protein secretion of the exocrine portion of the pancreatic gland in the anesthetized dog and rat. In the dog, no change in the concentration of bicarbonate in the pancreatic fluid was obtained.

In vitro studies of guinea pig ileum and in vivo studies of dog duodenum, ileum and transverse colon have shown increased gastrointestinal motility, which lessens in a distal direction.

A variable effect upon gastric acid and fluid production in the unanesthetized dog was seen after sincalide injection alone. In combination with either a gastrin-like tetrapeptide or histamine, an augmentation in the response to the latter two compounds was found. Gastric acid secretion was seen in the anesthetized rat.

Intravenous injection of doses of 0.004 to 64 mcg/kg of sincalide to unanesthetized dogs produced no gross cardiovascular changes at the lower doses, but transient tachypnea, hypotension, increased pulse pressure, and bradycardia were observed at doses of 0.064 and 0.256 mcg/kg. Similar effects, some persisting for more than 15 minutes, were seen at the 1.0 to 64 mcg/kg dose levels. After 64 mcg/kg primary A-V block lasting less than one minute was seen in one dog.

Doses of up to 3.75 mcg/kg of sincalide to pregnant rats and hamsters failed to cause contraction of the uteri, although all were sensitive to subsequent administration of oxytocin.

Immunological studies did not demonstrate any antibody production or immediate or delayed hypersensitivity reaction.

17 SUPPORTING PRODUCT MONOGRAPHS

KINEVAC® (sincalide), powder for solution, 5 mcg/vial, submission control number 256771, Product Monograph, Bracco Imaging Canada. (MAR 1, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

SINCALIDE FOR INJECTION

Sincalide for Injection

Read this carefully before you start taking **SINCALIDE FOR INJECTION** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SINCALIDE FOR INJECTION**.

What is SINCALIDE FOR INJECTION used for?

- SINCALIDE FOR INJECTION causes contraction of the gall bladder which causes it to release bile. This can be used to help in the examination of the bile ducts; as well as for collection of bile to diagnose health problems.
- SINCALIDE FOR INJECTION can be used together with another product (Secretin-sincalide test) to collect fluid and cells from the pancreas. This can be used to test for cancer of the pancreas.
- SINCALIDE FOR INJECTION can be used to treat a lack of movement in the intestines that sometimes occurs after surgery. This lack of movement can sometimes lead to a buildup of food which can block the intestines.
- SINCALIDE FOR INJECTION can be used to increase contractions in the intestines. This speeds up the movement of dyes used for diagnostic imaging.

How does SINCALIDE FOR INJECTION work?

SINCALIDE FOR INJECTION works by making the smooth (involuntary) muscles in the gastrointestinal tract contract.

What are the ingredients in SINCALIDE FOR INJECTION?

Medicinal ingredient: Sincalide

Non-medicinal ingredients: Arginine hydrochloride, hydrochloric acid (and/or sodium hydroxide), lysine monohydrochloride, mannitol, methionine, pentetic acid, sodium metabisulfite

SINCALIDE FOR INJECTION comes in the following dosage forms:

Powder for solution for injection, 5 mcg / vial

Do not use SINCALIDE FOR INJECTION if:

- you are allergic (hypersensitive) to sincalide or any or the other ingredients in SINCALIDE FOR INJECTION or component of the container.
- you must avoid meals that are high in fat, for example if you have: disorders of the pancreas, or gall bladder and its ducts; a gall bladder infection; gallbladder stones; appendicitis; organs with perforations (holes); infection or inflammation of the abdomen; ulcers, narrowing of the opening from the stomach to the small intestine, intestinal blockages or obstructions, any other blockages of the gastrointestinal tract; or severe abdominal pain.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SINCALIDE FOR INJECTION. Talk about any health conditions or problems you may have, including if you:

- have ulcers of the gastrointestinal tract.
- have intestinal bleeding.
- have indigestion or reflux disease.
- will have any procedures where imaging of the gastrointestinal tract may be required since SINCALIDE FOR INJECTION can increase the movement of the dyes used in those procedures.
- have gall stones, particularly small gall stones which can become stuck in the bile ducts after you have been given SINCALIDE FOR INJECTION.
- are pregnant or planning to become pregnant. SINCALIDE FOR INJECTION may cause spontaneous abortion or premature labour if taken while pregnant.
- are breastfeeding or planning to breastfeed.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take SINCALIDE FOR INJECTION:

SINCALIDE FOR INJECTION will always be used in a hospital or clinic and will be given to you by a specially trained and qualified healthcare professional. They will tell you anything you need to know for its safe use.

Usual dose:

Your doctor will decide the dose that is best for you and for the type of procedure to be performed.

Overdose:

The symptoms of overdosage with SINCALIDE FOR INJECTION are likely to be mild and of short duration. Symptoms include abdominal discomfort, cramps, nausea, vomiting and diarrhea. Dizziness and flushing may also occur.

If you think you, or a person you are caring for, have received too much SINCALIDE FOR INJECTION, contact a healthcare professional, hospital emergency department, or regional poison control center immediately, even if there are no symptoms.

What are possible side effects from using SINCALIDE FOR INJECTION?

These are not all the possible side effects you may have when taking SINCALIDE FOR INJECTION. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- abdominal pain, cramps
- an urge to have a bowel movement
- bitter taste in the mouth
- headache
- flushing, sweating
- pain at the injection site
- shaking of the hands
- sneezing

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypersensitivity (allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, nausea, vomiting, diarrhea, dizziness or fainting			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store vials of SINCALIDE FOR INJECTION powder at room temperature (15° - 30°C).

Keep out of reach and sight of children.

If you want more information about SINCALIDE FOR INJECTION:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.avirpharma.com), or by calling 1-888-430-0436.

This leaflet was prepared by:

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