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GE Healthcare

SONAZOID™

16 microlitre/vial

NAME OF THE MEDICINAL PRODUCT

Sonazoid powder and solvent for dispersion for injection
16 microlitre per vial

QUALITATIVE AND QUANTITATIVE COMPOSITION

Perfluorobutane microbubbles 8 microlitre per ml. Following reconstitution in 2 ml solvent according to instructions 1ml of the dispersion contains 8 microlitre perfluorobutane in microbubbles.

Excipient: Hydrogenated egg phosphatidylserine sodium

For a full list of excipients, see Pharmaceutical particulars.

PHARMACEUTICAL FORM

Powder and solvent for dispersion for injection.

The reconstituted medicinal product is a white dispersion.

Sonazoid is a freeze-dried drug product that is suspended in the provided reconstitution solvent before use. It is supplied as a kit containing:

1 vial of freeze-dried powder

1 ampoule with sterile water for reconstitution

1 filter spike

The pH of the reconstituted product is 5.7-7.0

Osmotic ratio in reconstituted drug product is 0.9-1.1 (compared to isotonic sodium chloride solution)

CLINICAL PARTICULARS

Therapeutic indications

This medicinal product is for diagnostic use only.

Sonazoid is an ultrasound contrast agent for use in vascular phase and Kupffer phase for ultrasonic imaging of focal hepatic lesions.

Posology and method of administration

This medicinal product should always be given by a physician or other qualified health personnel.

The usual adult dosage is up to one vial of the product containing 16 microlitre of perfluorobutane (PFB) microbubbles (MB) suspended in 2 ml of the accompanying sterile water for reconstitution to make a 8 microlitre/ml suspension. The product is for intravenous use only and the usual dosage is as per the table below.

Before administering Sonazoid, see Special precautions for disposal and other handling for instructions for reconstitution and use.

The reconstituted product is for intravenous use. No special preparation of the patient is required. Ultrasound imaging must be performed during injection of Sonazoid as optimal contrast effect is obtained immediately after administration. The intravenous line must be flushed immediately with 5-10 ml sodium chloride 0.9% solution for injection to ensure complete administration of the contrast agent.

The recommended clinical dose is 0.12 microlitre PFB microbubbles/kg body weight (is equivalent to 0.015 ml/kg as a suspension).

Refer to the table below for weight-based dosages.

Body Weight (kg)		40	50	60	70	80	90	100
Dosage	Suspension (ml)	0.60	0.75	0.90	1.05	1.20	1.35	1.50
	PFB microbubbles (microlitre)	4.8	6.0	7.2	8.4	9.6	10.8	12.0

Use in elderly

The usual /proposed dose for adults can be used.

Paediatric use

The safety of this product has not been established in the paediatric population (no data are available).

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use.

The possibility of hypersensitivity, including serious, life-threatening anaphylactoid reaction / anaphylactoid shock should always be considered. Advanced life support facilities should be readily available.

Sonazoid contains a chicken egg-derived surfactant (hydrogenated egg phosphatidylserine sodium; H-EPSNa). In patients with a history of allergy to eggs or egg products, use Sonazoid only if the benefit clearly outweighs the potential risk.

Care should be taken in patients with right to left arteriovenous cardiac or pulmonary shunt, as Sonazoid enters the circulation directly without passing through the lungs.

Sonazoid should be administered with care in patients with unstable heart conditions or serious coronary arterial disease. Sonazoid should be administered with care in patients with serious pulmonary disease as this product is primarily excreted by the lungs.

Ultrasonography with Sonazoid may be negatively affected by excessive intraabdominal gas following laparoscopy, barium swallow exam using a foaming agent or other gastrointestinal examinations.

Interaction with other medicinal products and other forms of interaction

Drug interaction studies have not been performed in humans. A drug interaction study performed in vitro did not show any effects of Sonazoid on the most common anti-thrombotic medicinal products, using Sonazoid at concentrations corresponding to the recommended clinical dose.

Fertility, pregnancy and lactation

The safety of Sonazoid for use during human pregnancy has not been established. Animal studies did not indicate reproductive toxicity (see Preclinical safety data). Sonazoid should not be used in pregnancy unless benefit outweighs risk.

It is not known whether Sonazoid is excreted in human milk. It has not been established whether lactation can affect children. Further, Sonazoid administration should be avoided in lactating mothers and, if it is to be administered out of necessity, cessation of lactating should be advised.

Effects on ability to drive and use machines

Not relevant

Undesirable effect

Adverse reactions to Sonazoid are usually non-serious. Reported adverse reactions following the use of Sonazoid were mild to moderate with subsequent full recovery. The most commonly noted adverse reactions were headache, diarrhoea, nausea, vomiting, abdominal pain, transient altered taste, and fever.

Cases of hypersensitivity reactions have been reported uncommonly, anaphylactoid reaction and anaphylactoid shock have been reported.

The frequencies of undesirable effects are defined as follows:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

The listed frequencies are based on the clinical trial database for Sonazoid comprising more than 2,500 patients.

The following undesirable effects are recognised for Sonazoid:

Immune system disorders

Uncommon: Hypersensitivity, including mild allergic reaction, conjunctivitis, rhinitis, rash, pruritus

Not known: Anaphylactoid shock, anaphylactoid reaction

Nervous system disorders

Uncommon: Headache; dizziness, dysgeusia

Gastrointestinal disorders

Uncommon: Diarrhoea, vomiting, nausea, abdominal pain

Vascular disorders

Uncommon: Flushing

General disorders and administration site conditions

Uncommon: Injection site pain, injection site reaction, pyrexia.

Results from clinical trials indicate no age-related increase in the incidence of adverse events or adverse drug reactions in elderly patients.

Overdose

Not relevant

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Ultrasound contrast agent
ATC code: V08D A06

The active ingredient of this product is PFB microbubbles, which are capable of crossing the pulmonary capillary bed after intravenous injection to reach the left side of the heart and subsequently circulate throughout the body. The radiated ultrasonic waves are efficiently backscattered by the surface of the microbubbles, thus enhancing the blood vessel images. In the diagnosis of hepatic mass lesions, differential diagnosis (qualitative diagnosis) can be performed by way of vascular imaging to visualize vessels in, on, and around a lesion immediately after administration. In addition, part of the microbubbles in this product are taken up by the reticuloendothelial system (Kupffer cells in the case of the liver), thereby enhancing the contrast between healthy tissue and tumours, which do not possess a reticuloendothelial system, from 5 to 10 minutes after administration. This makes it possible to diagnose the presence of tumours in what is known as Kupffer-phase imaging.

The product's contrast effect is obtained by vascular-phase imaging immediately after administration and Kupffer-phase imaging (hepatic parenchymal enhancement) about 10 minutes after administration. To ensure proper imaging in the Kupffer phase, imaging should be suspended after the vascular phase to prevent disintegration of the microbubbles. The presence of Kupffer cells within hepatic mass lesions may make it difficult to distinguish the focus in Kupffer-phase imaging following administration of the product, so pre-contrast ultrasound images should be used as a reference.

Pharmacokinetic properties

The concentration of PFB in the blood upon a single intravenous administration of the product to healthy adults at doses of 0.024 microlitre MB/kg, 0.12 microlitre MB/kg (clinical dosage), and 0.60 microlitre MB/kg (0.003 ml/kg, 0.015 ml/kg, and 0.075 ml/kg respectively as a suspension) attenuated rapidly after administration. The PFB concentration attenuated in two phases for the clinical dose of 0.12 microlitre MB/kg, with a half-life of 2.7 minutes in the 2-15-minute post-administration phase, and a half-life of 7.3 minutes in the 15-30 minute post-administration phase. Furthermore, the PFB concentration fell below the detection limit at 60 minutes after administration.

Administered PFB is excreted in expired air. The concentration of PFB in expired breath upon a single IV administration of the product to healthy adults at doses of 0.024 microlitre MB/kg, 0.12 microlitre MB/kg (clinical dosage), and 0.60 microlitre MB/kg (0.003 ml/kg, 0.015 ml/kg, and 0.075 ml/kg respectively as a suspension) was measured. All of the concentrations of PFB in expired breath were dose-dependent at the time they were measured. At the clinical dose of 0.12 microlitre MB/kg, the PFB concentration reached C_{max} at 6 minutes after administration and fell below the detection limit at 2 hours after administration. At a dose of 0.024 microlitre MB/kg, the concentration of PFB in expired breath was below the detection limit for all subjects.

Clinical studies

Clinical-sponsored studies have effectively demonstrated the safety and efficacy of Sonazoid in humans during the clinical development. Several clinical studies have confirmed these conclusions.

Phase III clinical trial DD723-04 is a confirmatory study of efficacy and safety in patients with focal hepatic lesions by comparing images from unenhanced and contrast enhanced ultrasonography (CEUS) about differential diagnosis (vascular phase imaging) and detection of lesion presence (Kupffer phase imaging). A total of 193 subjects were administered with a single dose of 0.12 µL MB/kg Sonazoid and analysed.

With regard to the vascular phase imaging primary endpoint, the agreement rate between diagnoses from CEUS examinations and the final (reference) diagnoses was good (88.9%), and the difference in the agreement rate compared with that of the diagnoses from unenhanced ultrasound examinations was 20.5% (95% C) = 13.5-27.6%), confirming a significant improvement in differential diagnosis due to Sonazoid (McNemar test, p <0.001).

For Kupffer-phase imaging, the results of comparing the number of hepatic lesions detected in pre-contrast examinations with the number of lesions detected in the pre- plus post-contrast examinations in relation to the number of lesions noted at the time of entry revealed that the proportion of cases in which the score increased for the pre- plus post-contrast was higher than for pre-contrast scans alone, and the difference was statistically significant (Wilcoxon signed-rank test, p <0.001).

Additionally, safety was confirmed, with no deaths, or serious or severe AEs observed.

In conclusion, results of that study DD723-04 demonstrated the safety and efficacy of Sonazoid in differential diagnosis of lesions in vascular phase imaging and diagnosis of the presence of lesions by Kupffer phase imaging.

Phase III clinical trial DD723-05 was carried out in 36 subjects with hepatocellular carcinoma at multiple centres to investigate the efficacy of Sonazoid in assessing effectiveness of radio frequency ablation (RFA) treatment, by comparing CEUS and computed tomography (CT) findings. Sonazoid was administered as a single i.v. dose of 0.12 mL MB/kg.

To investigate the post-RFA treatment effect, perfusion status and adequacy of safety margins around lesions of interest were assessed as primary endpoints, and CEUS findings were compared to those from contrast-enhanced CT.

In evaluating the effect of treatment with RFA, the rates of consistency in assessments of residual lesion perfusion by from CEUS (assessment by 3 blinded readers) and contrast-enhanced CT (assessment by the on-site investigator) were 93.3, 96.3 and 93.1% for the respective blinded readers, with k coefficients of 0.714, 0.836 and 0.633, respectively. The rates of consistency in assessments of the ablated safety margin, the other primary endpoint, by CEUS (assessment by 3 blinded readers) with those by contrast-enhanced CT (assessment by the on-site investigator) were 93.3, 92.6 and 93.1% for the respective blinded readers, with k coefficients of 0.851, 0.851 and 0.858, respectively. Therefore, for both primary endpoints, good consistency was obtained between contrast-enhanced ultrasound and CT assessments.

These results indicate that Sonazoid will be useful in the evaluation of post-RFA treatment effects, with CEUS diagnostic efficacy with Sonazoid similar to contrast-enhanced CT.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

In repeated dose studies in rats, transient inflammatory findings in the lungs were observed at all dose levels. Similar findings were not observed in single dose studies in rats, neither in single- or repeated dose studies in dogs at dose levels ≥ 200 times the recommended clinical dose. Lung findings were considered to be of minimal clinical relevance, based on recommended clinical dose.

Some strains of rats and mice developed severe lesions in the caecal and caecocolic regions of the gut after intravenous injection of Sonazoid. Milder reactions were also observed in dogs. The mechanism of these lesions has been elucidated, and is not considered to constitute a risk to humans. The same lesions are also seen in mice and rats when other ultrasound contrast agents are injected and are, thus, considered as a "class effect".

PHARMACEUTICAL PARTICULARS

List of excipients

Powder

Hydrogenated egg phosphatidylserine sodium

Sucrose

Solvent

Water for Injection

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except the solvent provided.

Shelf life

3 years

Special precautions for storage

Do not store above 30°C. Do not freeze.

After reconstitution, use within 2 hours, as chemical and physical in-use stability has been demonstrated for 2 hours at room temperature (15-25 ºC).

Nature and content of container

Sonazoid is provided as a kit containing:

- One Type I glass vial containing 16 microlitre perfluorobutane microbubbles (freeze-dried dosage form). The vial is closed with a rubber stopper (latex-free) and sealed with an aluminium cap.
- One ampoule of Water for Injection (WFI) with a low content of multivalent cations
- One filter spike with 0.20 micrometer air filter and a 5 micrometer liquid filter

Special precautions for disposal and other handling

Before use examine the product to ensure that the container and closure have not been damaged.

Vials are intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation

After injecting the WFI from the accompanying ampoule into the vial and preparing the suspension, always use the accompanying filter spike to draw the product into the syringe. When drawing the product into the syringe and injecting it back into the vial, do so slowly to avoid excessive decompression/compression. The use of a solvent other than the accompanying reconstitution diluent may cause aggregates to form.

- Open the accompanying reconstitution solvent: Wipe the ampoule with an ethanol disinfectant swab before cutting to avoid contamination.
- Collect 2 ml of the accompanying WFI in an empty syringe.
- Insert the accompanying filter spike into the product (freeze-dried dosage form).
- Attach the syringe with WFI to the filter spike, inject 2 ml of the WFI into the vial, and then immediately shake for one minute with the syringe still attached.
- Some of the WFI will remain in the dead space inside the filter spike, so draw the suspension into the syringe once then inject it back into the vial.
- Attach the syringe for collecting the suspension to the filter spike and draw the required dose into the syringe.

The suspension should be used within 2 hours of preparation.

Administration

- Use a syringe needle with a gauge of at least 22 G.
- Separation of the suspension may occur upon standing, so shake the product immediately before administration to ensure consistency of the contents.
- The administration route should typically be flushed with a small amount of isotonic sodium chloride solution (ISCS) immediately after administration of the product.
- After opening: The product vial is intended for single use only, and any remaining product must be discarded along with the filter spike after use.

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DATE OF REVISION OF THE TEXT

August 2021

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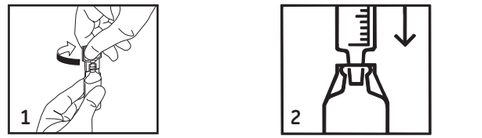
Instruction for use of sterile WFI ampoule



1. Twist the top of the ampoule

2. Place the syringe directly in the ampoule without using a cannula

An illustration of the reconstitution and withdrawal procedure for Sonazoid is shown below: