Summary Report of Benefit-Risk Assessment

SONAZOID POWDER AND SOLVENT FOR DISPERSION FOR INJECTION, 16 MICROLITRE PER VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Perfluorobutane (microbubbles)
Product Registrant	GE Healthcare
Product Registration Number	SIN16077P
Application Route	Abridged evaluation
Date of Approval	06 January 2021

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A INTRODUCTION

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

The active substance is perfluorobutane microbubbles, which are capable of crossing the pulmonary capillaries to enter 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 is obtained by vascular imaging to visualize vessels in, on and around a lesion after administration. Part of the microbubbles are taken up into the reticuloendothelial system (Kupffer cells in the liver) thereby enhancing the contrast between healthy tissues and tumours, which do not have reticuloendothelial system. This makes it possible to diagnose the presence of tumours in what is known as Kupffer-phase imaging.

Sonazoid is a powder for dispersion for injection containing 16 microlitres per vial of perfluorobutane microbubbles. Following reconstitution in 2 ml of solvent, 1 ml of the dispersion contains 8 microlitres of perfluorobutane microbubbles. Other ingredients are hydrogenated egg phosphatidylserine sodium and sucrose. An ampoule of sterile water for injection is supplied as the reconstitution solvent with the Sonazoid.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, perfluorobutane, is manufactured at F2 Chemicals, Lancashire, United Kingdom. The drug product, Sonazoid powder and solvent for dispersion for injection 16 microlitre per vial, is manufactured at GE Healthcare AS, Oslo, Norway. The solvent, sterile water for injections, is manufactured by B. Braun Melsungen AG, Berlin, Germany.

Drug substance:

Adequate controls have been presented for the starting materials and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented were adequate to support the approved storage condition and re-test period. The packaging is seamless high-pressure cylinder made of standard chromium-molybdenum steel. The drug substance is approved for storage at 1-30°C with a re-test period of 60 months.

Drug product - Powder:

Sonazoid powder for injection is manufactured by aseptic processing. The raw materials are mixed, sterile-filtered and passed through a rotor/stator mixer with perfluorobutane gas to generate gas-filled microspheres. The microsphere dispersion is filled into Type I tubular glass vials and lyophilised.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines.

Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 36 months when stored at or below 30°C. The in-use period after opening is 2 hours when stored between 15°C to 25°C and is supported with appropriate data. The container closure system is a Type 1 tubular glass vial closed with bromobutyl rubber stopper, sealed with aluminium cap and polypropylene lid, supplied with 1 filter spike.

Drug product - Solvent:

The solvent-sterile water for injection is manufactured using sterile filtration. The process is considered to be a standard process. The manufacturing process utilises terminal sterilization.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and USP/Ph. Eur. monographs. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines.

The stability data submitted were adequate to support the approved shelf-life of 36 months when stored at or below 30°C. The container closure system is a blow moulded polyethylene ampoule.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Sonazoid for vascular phase and Kupffer phase ultrasonic imaging of focal hepatic lesions was based primarily on data from two pivotal phase III studies, DD723-04 and DD723-05.

Study DD723-04 was a phase III, multicentre, open-labelled study conducted to compare unenhanced ultrasound and contrast-enhanced ultrasound (CEUS) using Sonazoid in patients

with untreated focal hepatic lesions. The study aimed to determine the differential diagnosis and number of focal hepatic lesions based on vascular and Kupffer imaging respectively performed in harmonic B-mode. A total of 194 subjects in the study were administered a single dose of Sonazoid 0.12 µL MB/kg. Unenhanced ultrasound and CEUS were performed as separate examinations. Based on the evaluation of ultrasound images, the efficacy of Sonazoid in differentially diagnosing lesions (agreement with final diagnosis) and detecting the presence of lesions (lesion detection) was determined from vascular and Kupffer imaging respectively.

For vascular imaging, the primary endpoint was based on the consistency of diagnosis of the lesions of interest with final diagnosis (agreement with final diagnosis) using unenhanced ultrasound and CEUS. Comparison of diagnoses made by CEUS and computerised tomography scan (CT scans), respectively with final diagnosis was assessed as a key secondary endpoint. For Kupffer imaging, the primary endpoint was the comparison of unenhanced ultrasound and CEUS with regard to lesions visualised in the reference exams at the time of study entry. Comparison of lesion detection results with CT scan was assessed as a key secondary endpoint. Lesions were assessed and scored with respect to the number of lesions confirmed at the time of study entry, and the scores were use as comparisons. The CT scan was conducted in the past month for malignant lesions and within 3 months for benign lesions in patients with untreated focal hepatic lesions. Based on literature[1] and the doubling time, it is reasonable to assume that the number of malignant lesions would remain constant within a month and benign lesions within 3-12 months window, hence the use of CT scans for comparison in the secondary endpoints was considered acceptable.

The main diagnosis at enrolment was hepatocellular carcinoma (HCC) (vascular imaging: 63.2%; Kupffer imaging: 62.8%) and metastatic hepatic carcinoma (vascular imaging: 20.0%; Kupffer imaging: 19.9%). Most of the subjects were male (67.9% - 68.1%) and more than half were aged 65 years and older (53.9% - 54.2%). Majority of subjects had only 1 lesion at enrolment (55.5% - 55.8%).

With regard to the vascular phase imaging primary endpoint, the consistency of diagnosis (agreement with final diagnosis) of CEUS (88.9%) was significantly higher than that for unenhanced ultrasound (68.4%; p <0.001), demonstrating the advantage of using Sonazoid for the differential diagnosis of lesions.

The key secondary endpoint of agreement rate of CEUS with the final diagnosis (88.9%) was significantly higher than that observed with the CT scan (80.5%; McNemar test, p=0.008). The methods used for final diagnosis in a small subgroup of 22/193 subjects were provided and consisted of contrast-enhanced CT scans (CECT), magnetic resonance imaging (MRI) scans, angiography, biopsy and surgery and were considered to be standard clinical practice. Taken together, comparison of diagnosis agreement with respect to the final diagnosis supported the efficacy in the overall population.

Sumary of Key Efficacy Results (DD723-04 Vascular Imaging)

	CEUS	**Unenhanced Ultrasound**	**Difference**
Agreement with final diagnosis	169/190 (88.9%)	130/190 (68.4%)	20.5% (p<0.001)
	CEUS	**CT Scan**	
	169/190 (88.9%)	153/190 (80.5%)	8.4% (p=0.008)

Reference:
1. An Chansik, Choi Youn Ah, Choi Dongil, Paik Yong Han, Ahn Sang Hoon, Kim Myeong-Jim, Paik Seung Woon, Han Kwang-Hyub and Pak Mi-Suk.Growth Rate of early-stage hepatocellular carcinoma in patients with chronic liver disease. Clin Mol Hepatol 2015 Sep; 21 (3): 279-286

The primary endpoint for Kupffer imaging was the comparisons of the number of focal hepatic lesions recorded at the time of study entry with the number of lesions detected in the unenhanced ultrasound and CEUS. The number of lesions detected in the unenhanced ultrasound and CEUS were scored against the number of known focal hepatic lesions at the time of study entry. The scores were categorised as 0, 1 or 2 if the ultrasound showed less, equal or more number of lesions respectively compared to the time of study entry. The overall proportion of CEUS cases with an increased score compared to unenhanced ultrasound was 30.9% (score increased from 0 to 1: 7.9%, 1 to 2: 13.6%, 0 to 2: 9.4%), while the proportion with a reduced score was 7.3% (score reduced from 1 to 0: 3.1%, 2 to 1: 4.2%, and 2 to 0: 0.0%). A statistically significant difference in score distribution was noted (Wilcoxon signed-rank test, p <0.001), demonstrating the improved ability of CEUS to detect the presence of lesions.

Kupffer imaging in subjects obtained by CEUS were compared with those obtained by CT scans for the key secondary efficacy endpoint. The overall proportions of subjects in whom the score increased for CEUS compared to the number recorded by CT scans was 26.7%. In contrast, the proportions of cases in which the score decreased for CEUS compared to CT scan was 15.2%. A statistically significant difference was seen in the distribution of scores for the number of focal hepatic lesions (Wilcoxon signed-rank test, p = 0.008). There were 22 new lesions detected in CEUS compared to study entry. Of the 22 lesions, 16 lesions underwent diagnosis post study using standard methods such as CT Scans, MRI and biopsy and 12 lesions were confirmed. Lesions detected by CEUS were mostly true lesions (12/16) as verified by other standard methods.

Summary of Key Efficacy Results (DD723-04 Kupffer Imaging)

Scores for Number of Lesions	**Percentage of CEUS cases with increased score compared to Unenhanced ultrasound**	**Percentage of CEUS cases with increased score compared to CT Scan**
Increase from 0 to 1	7.9%	2.6%
Increase from 1 to 2	13.6%	19.4%
Increase from 0 to 2	9.4%	4.7%
p value	p<0.001	p=0.008

DD723-05 was an exploratory, phase III multicentre study conducted to assess the efficacy of Sonazoid in the evaluation of the therapeutic response after radiofrequency ablation (RFA) treatment of HCC. A total of 36 subjects were enrolled and received 2 single doses of 0.12 µl MB/kg Sonazoid, one before and one after conducting RFA.

The primary endpoint was the agreement rate of CEUS evaluated by blinded readers and CECT evaluated by on-site investigators for post-RFA treatment effect on the perfusion status and adequacy of safety margins around lesions of interest. The agreement rate of the evaluations using CEUS versus CECT (both evaluated by on-site investigators) was the key secondary endpoint.

The majority of subjects were male (69.4%) and < 65 years old (19.4%). The diagnosis at study entry was HCC (100%) and majority of RFA-scheduled lesions were greater than 1 cm but less than 2 cm (62.9%).

High agreement rates were obtained for the evaluation of residual perfusion using CEUS (blinded readers) versus CECT (investigators), with agreement rates of 93.3%, 96.3% and

93.1% respectively for each of the 3 blinded readers. High agreement rates were also obtained for the evaluation of an adequate safety margin using CEUS (blinded readers) versus CECT (investigators), with agreement rates of 93.3%, 92.6% and 93.1%, respectively for each of the 3 blinded readers. For both primary endpoints, good consistency was obtained between CEUS and CECT.

The results for the secondary endpoints concerning the evaluation of perfusion and safety margin using CEUS versus CECT (both by investigators) were high, with an agreement rate of 97.1% for perfusion, and an agreement rate of 97.1% for safety margin. Therefore, CEUS is able to evaluate post-RFA treatment effect with good consistency compared to CECT.

Summary of Key Efficacy Results (DD723-05)

Concordance rate between CEUS and CT Scan	**Blinded Reader 1**	**Blinded Reader 2**	**Blinded Reader 3**
Perfusion Assessment	93.3%	96.3%	93.1%
Safety Margin Assessment	93.3%	92.6%	93.1%

Overall, the results of the two studies adequately supported the efficacy of Sonazoid as an ultrasound contrast agent for use in imaging of focal hepatic lesions.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of Sonazoid was based primarily on safety data from the Phase II and Phase III studies in patients with hepatic mass lesion and/or hepatocellular carcinoma. The analysis included a total of 397 subjects from 3 studies (DD723-02, DD723-04 and DD723-05). In DD723-02, 56 subjects received 0.024 µl MB/kg, 57 subjects received 0.12 µl MB/kg, and 55 subjects received 0.36 µl MB/kg of Sonazoid. All subjects in DD723-04 received single dose of 0.12 µl MB/kg Sonazoid while subjects in DD723-05 received 2 doses of 0.12 µl MB/kg Sonazoid.

Summary of Safety Profile

	DD723-02 N=168	**DD723-04 N=193**	**DD723-05 N=36**	**Total N=397**
Subjects with AEs	34 (20.2%)	95 (49.2%)	31 (86.1%)	160 (40.3%)
AEs	66	239	79	384
Relationship				
Related	4 (6.06%)	3 (3.92%)	2 (2.53%)	29 (7.55%)
Not Related	62 (93.94%)	216 (90.38%)	77 (97.4%)	355 (92.45%)
Intensity				
Mild	60 (90.91%)	230 (96.23%)	78 (98.73%)	368 (95.8%)
Moderate	6 (9.09%)	9 (3.77%)	1 (1.27%)	16 (4.17%)
Serious AEs	0	0	1 (1.27%)	0
Withdrawals due to AE	0	0	0	0
Deaths	0	0	0	0

For the combined studies, a total of 160 (40.3%) subjects experienced 384 adverse events (AEs).The most common AE is diarrhoea, headache, nausea, vomiting, abdominal pain and

pyrexia, however, most AEs were assessed by the investigators as having no reasonable possibility of being related to Sonazoid across all treatment groups. The majority of AEs observed with Sonazoid treatment were mild to moderate in severity with subsequent full recovery.

No serious AEs (SAEs) were recorded during the AE observation period (up to 72 hours after administration) in the clinical studies. In study DD723-05, 2 SAEs were reported in 1 subject ('hypotension' and 'consciousness loss') during the SAE observation period (up to 7 days after administration) but after conclusion of the AE observation period. This was considered unrelated to study treatment. There were no deaths or withdrawals due to AEs.

Overall, Sonazoid presented an acceptable safety profile for the target patient population given the diagnostic use. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Primary liver cancer is one of a few malignant tumours in which the etiological and pathogenic process of chronic viral hepatitis as a contributing factor of hepatocellular carcinoma is understood, and high-risk groups have been identified. The treatment and prognosis of metastatic liver cancer often depends on the pathological characteristics of the primary tumour. Standard clinical practice for diagnostic imaging of lesions usually consists of ultrasound, CECT scans, MRI scans and angiography. Sonazoid was developed as a contrast agent in ultrasound imaging for differential diagnosis of focal hepatic lesions.

The efficacy of Sonazoid was demonstrated in 2 pivotal studies. CEUS had a higher agreement rate with the final diagnosis compared to the unenhanced ultrasound in pivotal trial DD723-04 using vascular imaging. More lesions were identified in CEUS compared to the unenhanced ultrasound when compared to lesions at study entry using Kupffer imaging. Similarly, study DD723-05 reported the high agreement rates of CEUS with CECT pertaining to the evaluation of the treatment effect of RFA for HCC. Taken in totality, the overall evidence was adequate to support the use of Sonazoid as an ultrasound contrast agent for use in ultrasonic imaging of focal hepatic lesions.

The safety profile of Sonazoid was considered to be acceptable relative to the benefits. The most common adverse events such as headache, diarrhoea, nausea, vomiting were mild to moderate in severity with subsequent full recovery. Most AEs were assessed by the investigators as having no reasonable possibility of being related to Sonazoid across all treatment groups. Appropriate warnings have been included into the local package insert.

Overall, the benefit-risk profile of Sonazoid as an ultrasound contrast agent for the diagnosis of focal hepatic lesions was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Sonazoid as an ultrasound contrast agent for use in vascular phase and Kupffer phase imaging of focal hepatic lesions was deemed favourable and approval of the product registration was granted on 06 January 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

1194791 SGP

1194791

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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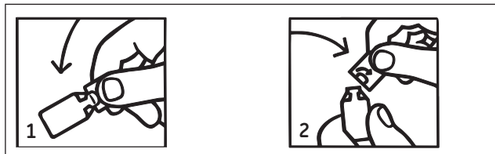
Sonazoid is a trademark of GE Healthcare.

GE and the GE Monogram are trademarks of General Electric Company.

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: