Sonazoid™

An ultrasound contrast agent for use in vascular phase and Kupffer phase for ultrasonic imaging of focal hepatic lesions[1]

For Norway only.

Prescribing information can be found at the end of this presentation

Imagination at work

04-2020 | JB25357NO(2)

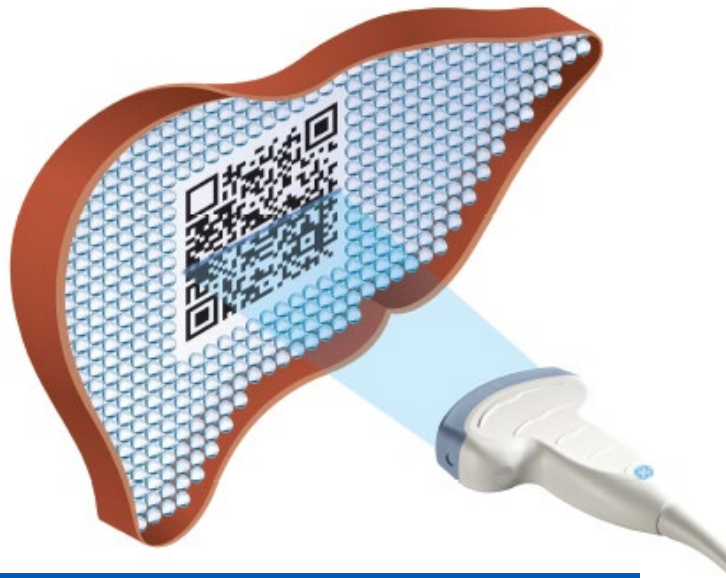
Reference: 1. Sonazoid SmPC Norway 05/2019.

SONAZOID™
PERFLUOROBUTANE MICROBUBBLES

Menu

Sonazoid™

Enabling diagnosis of focal liver lesions in vascular-phase imaging and enhanced detection of lesions in Kupffer-phase imaging[1]



Administration of Sonazoid enables vascular-phase imaging immediately and Kupffer-phase imaging (hepatic parenchymal enhancement) from about 10 minutes after injection[1]

Reference: 1. Moriyasu & Itoh. Am J Roentgenology 2009; 193: 86-95.

Current approval status for Sonazoid

Countries	Indication	Source
Japan	Contrast enhancement in ultrasonography of the following: focal liver lesions, focal breast lesions	Sonazoid SmPC dated March 2020
Korea	Contrast enhancement in ultrasonic imaging of hepatic tumor lesions in adult patients	Sonazoid SmPC dated March 2019
Norway	Sonazoid is an ultrasound contrast agent for use in vascular phase and Kupffer phase for ultrasonic imaging of focal hepatic lesions	Sonazoid SmPC dated May 2019[1]
Taiwan	Sonazoid is an ultrasound contrast agent, for use in liver ultrasonography to classify the focal liver lesion.	Sonazoid SmPC dated Sep 2018
China	Sonazoid is an ultrasound contrast agent for use in ultrasonic imaging of vascular/ Kupffer phase of focal hepatic lesions	Sonazoid SmPC dated July 2018

Reference:
1. Sonazoid SmPC Norway 05/2019.

CHAPTER 1

Approved indication

Indication approved by NOMA*[1]

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.

Please refer to PI at the end of the presentation for approved wording in Norwegian

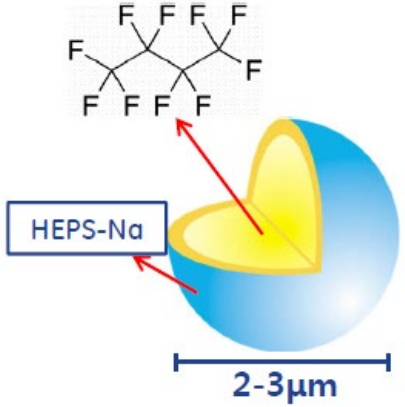
*Norwegian Medicines Agency

Reference: 1. Sonazoid SmPC Norway 05/2019.

CHAPTER 2

Characteristics of Sonazoid microbubbles

Sonazoid – composition



Like all ultrasound contrast agents Sonazoid consists of gas-filled microbubbles[1]

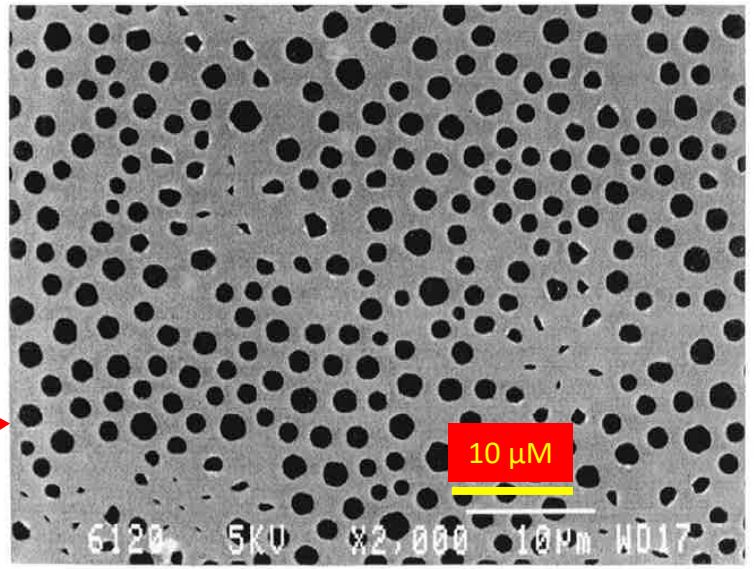
- Membrane is hydrogenated egg phosphatidylserine sodium (HEPSNa)
- The gas is perflubutane/perfluorobutane

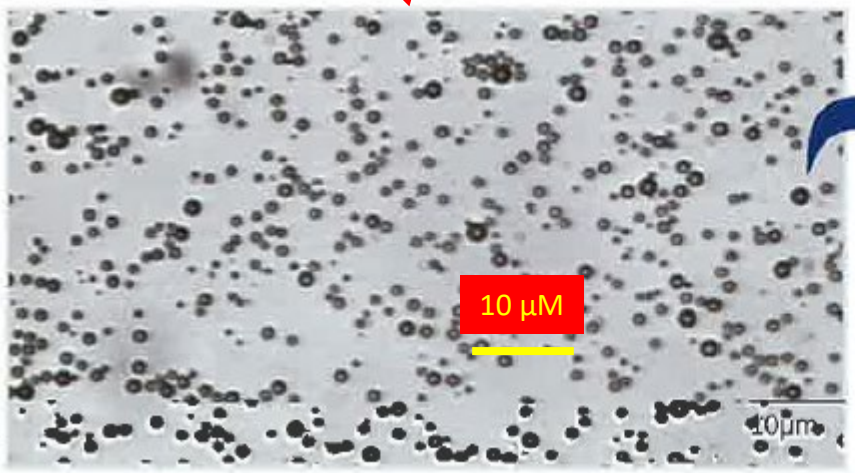
Produced in GE's factory at Storo, Oslo:
Each vial contains a freeze-dried 'cake' of pre-formed microbubbles

Reference: 1. Sonazoid SmPC Norway 05/2019.

Sonazoid characteristics[1]

The freeze-dried 'cake' containing very small pre-formed microbubbles is mixed with 2 mL WFI to make a ready-for-use suspension containing 16 µL microbubbles (8 µL/mL)





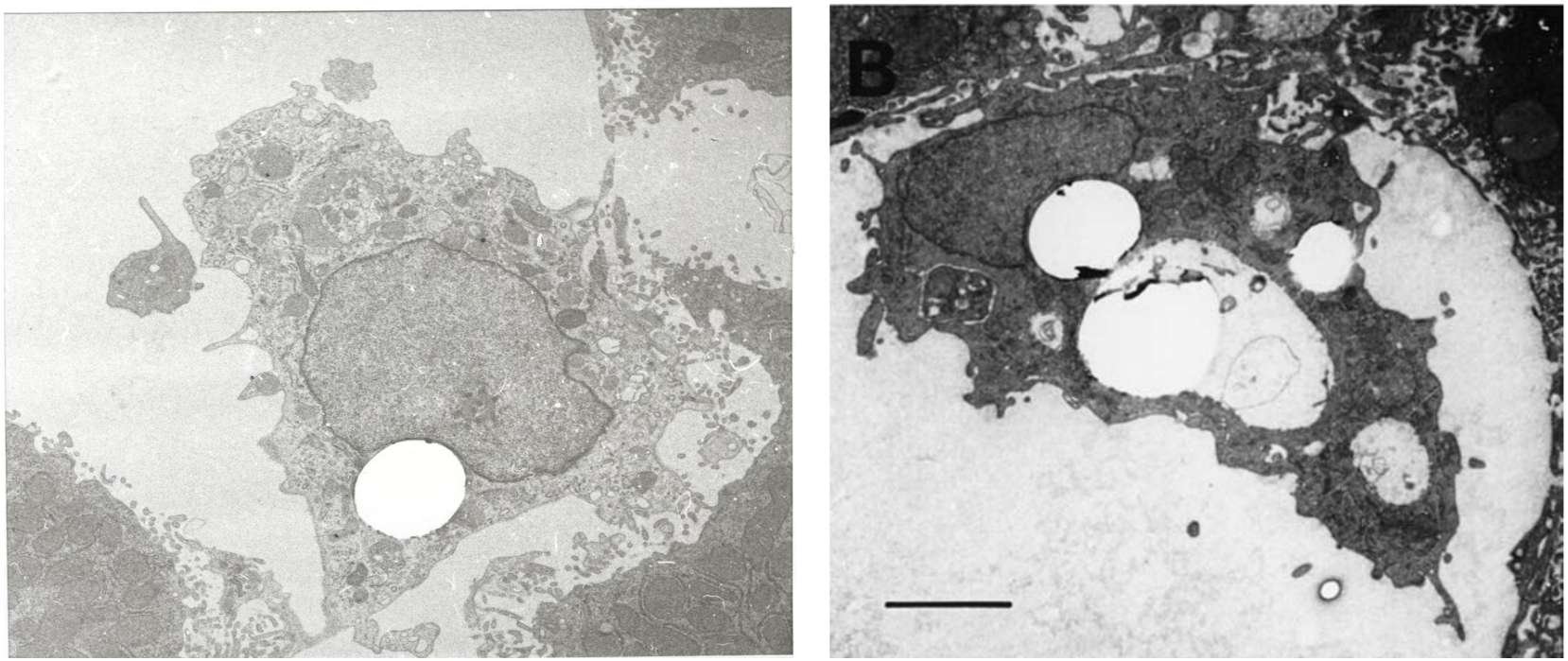
Hydrogenated egg phosphatidylserine sodium

Images courtesy GE Healthcare
WFI: Water for Injection

Reference:
1. Sonazoid SmPC Norway 05/2019.

Liver imaging with Sonazoid[1,2]

- In vacular-phase Sonazoid behaves similarly to other microbubbles (MBs)
- Sonazoid is taken up exclusively by the Kupffer cells and not by parenchymal, stellate or endothelial cells
- MBs are stable after uptake & give long-lasting enhancement



Electron micrographs of two rat liver Kupffer cells following injection of 50 l microbubbles/kg b.w. : Figure 1A shows a Kupffer cell that has taken up one microbubble, Fig. 1B shows a Kupffer cell that has taken up three microbubbles.[2]

References
1. WFUMB-EFSUMB. Guidelines 2012 Med & Biol 2013; 39: 187-201. http://dx.doi.org/10.1016/j.ultrasmedbio.2012.09.002 Last accessed on: 02/2020
2. Kindberg, Tolleshaug, Roos, Skotland: Cell Tissue Res. 312 (2003) 49-54

Characteristics of Sonazoid

Efficacy in terms of characterizing liver lesions as benign/malignant:

- During vascular-phase[2]
- During post-vascular-phase (late-phase/Kupffer-phase) imaging properties due to trapping in the sinusoids and Kupffer cell uptake[1,2]
- Microbubbles are robust [3]

References:
1. Sonazoid SmPC Norway 05/2019.
2. WFUMB-EFSUMB. Guidelines 2012 Med & Biol 2013; 39: 187-201. http://dx.doi.org/10.1016/j.ultrasmedbio.2012.09.002 Last accessed on: 02/2020
3. Alter J *et* al. Ultrasound in Med & Biol 2009; 35: 976-84.

CHAPTER 3

Sonazoid reconstitution

Sonazoid kit

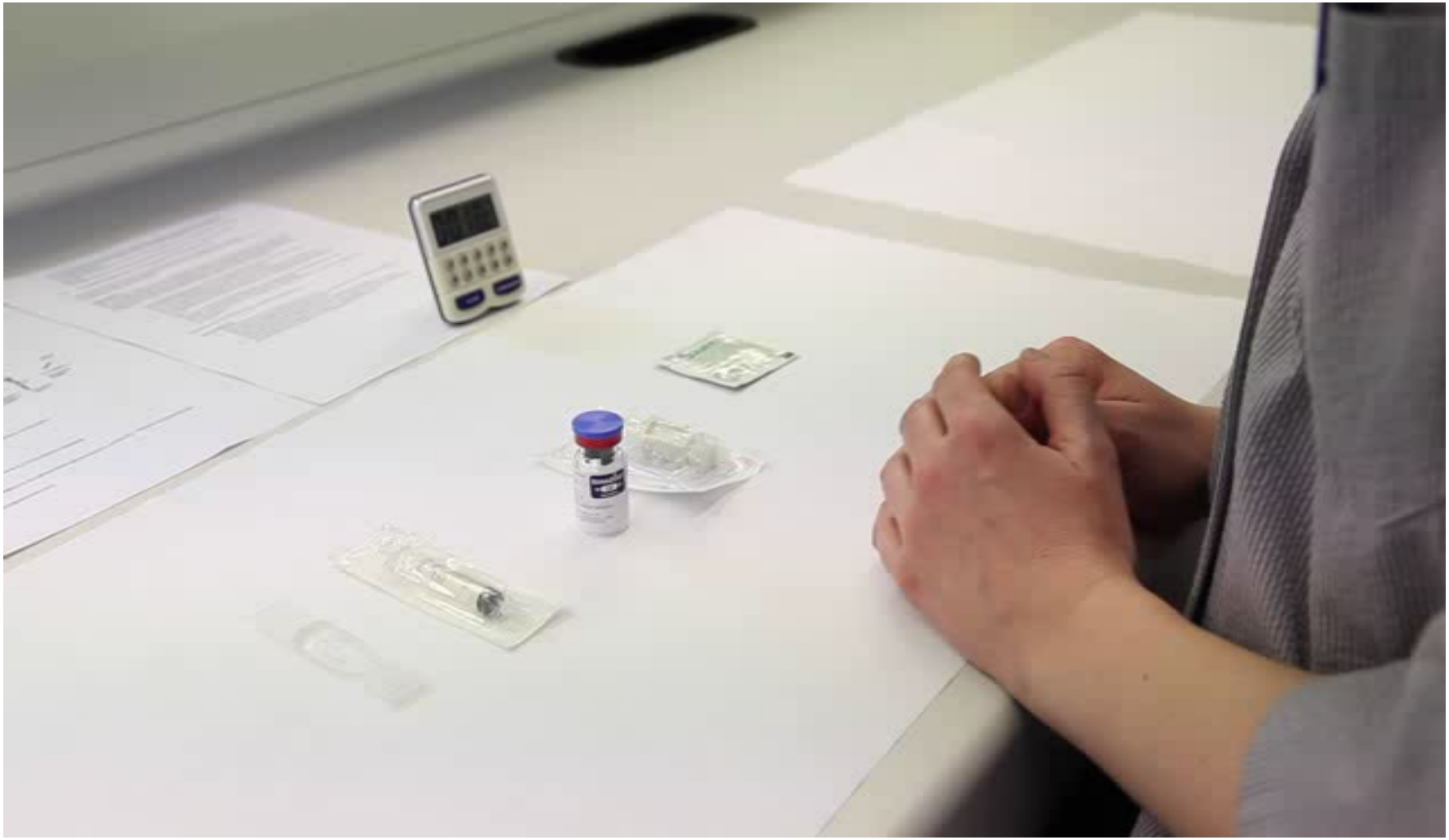
Each kit contains:[1]

- 10-mL glass vial of freeze-dried product manufactured by GE Healthcare in Oslo
- 1 ampoule with sterile water for reconstitution
- 1 filter spike

Component	Function	Content per vial	Concentration after reconstitution with 2 mL of Water for Injection	Osmotic ratio (compared to isotonic saline)
Perfluorobutane microbubbles	Active ingredient	16 µL perfluorobutane microbubbles in freeze-dried powder	8 µL perfluorobutane microbubbles/mL	0.9-1.1
Hydrogenated egg phosphatidylserine sodium salt	Stabiliser	0.2 mg	0.1 mg/mL	
Water for Injection	Reconstitution solvent	10 mL	Not applicable	Not applicable

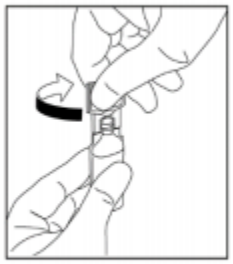
Table adapted from reference: 1. Sonazoid SmPC Norway 05/2019.

Reconstitution procedure for Sonazoid

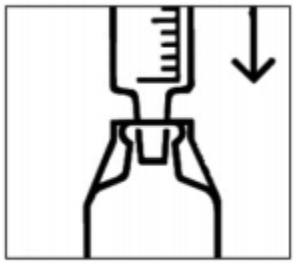


Instructions for reconstitution of Sonazoid[1]

Illustrasjon for bruk av ampullen med sterilt vann

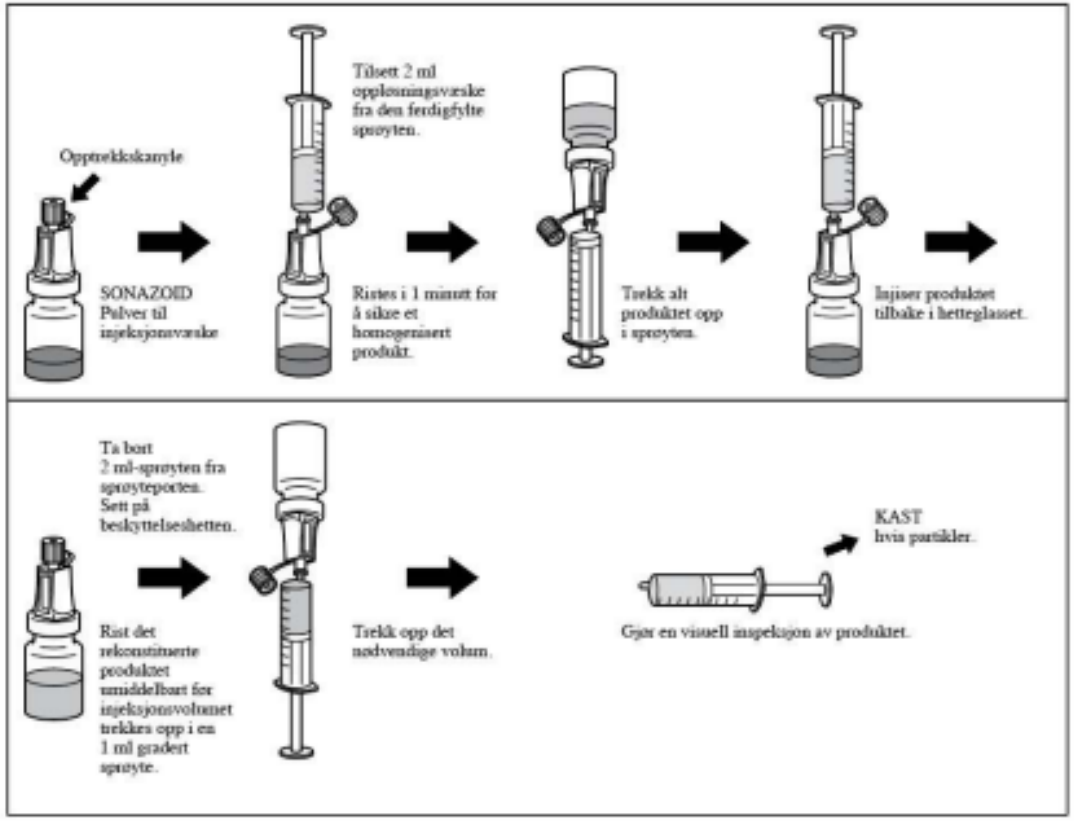


Vri av toppen på ampullen



Sett sprøyten direkte i ampullens åpning uten å bruke kanyle.

En illustrasjon av tilberedning og opptrekksprosedyre for Sonazoid er vist nedenfor:



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

NB avoid excess pressure as this will destroy the microbubbles!

Dosing of Sonazoid

The recommended clinical dose is 0.12 microlitres perfluorobutane microbubbles/kg body weight. (Each 2-mL vial contains 16 µL MB)[1]

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**
	Perfluorobutane microbubbles (microlitres)	**4.8**	**6.0**	**7.2**	**8.4**	**9.6**	**10.8**	**12.0**

Table adapted from SmPC[1]

Reference: 1. Sonazoid SmPC Norway 05/2019.

CHAPTER 4

Sonazoid imaging aspects

Ultrasound equipment and Sonazoid

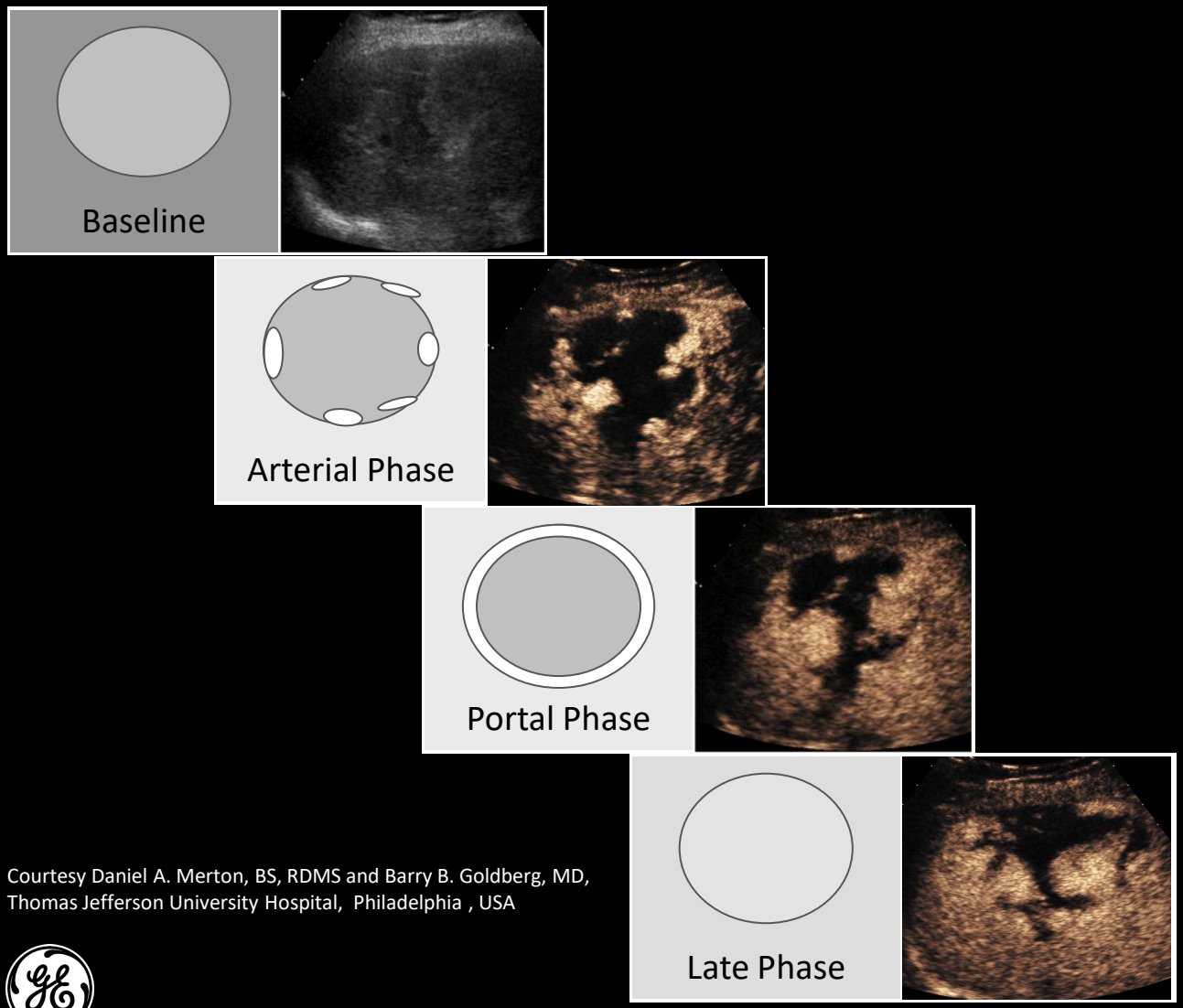
- To obtain best image quality with Sonazoid, the imaging equipment must be optimized
- Unless the imaging system already has a “Sonazoid pre-set” it is recommended to ask the vendor's local application specialist to develop and install a Sonazoid pre-set for the machine
- Sonazoid imaging is performed at slightly higher acoustic power (or higher Mechanical Index) than SonoVue imaging since Sonazoid bubbles are more robust[1]

Reference: 1. Alter J *et al*. Ultrasound in Med & Biol 2009; 35: 976-84.

CHAPTER 5

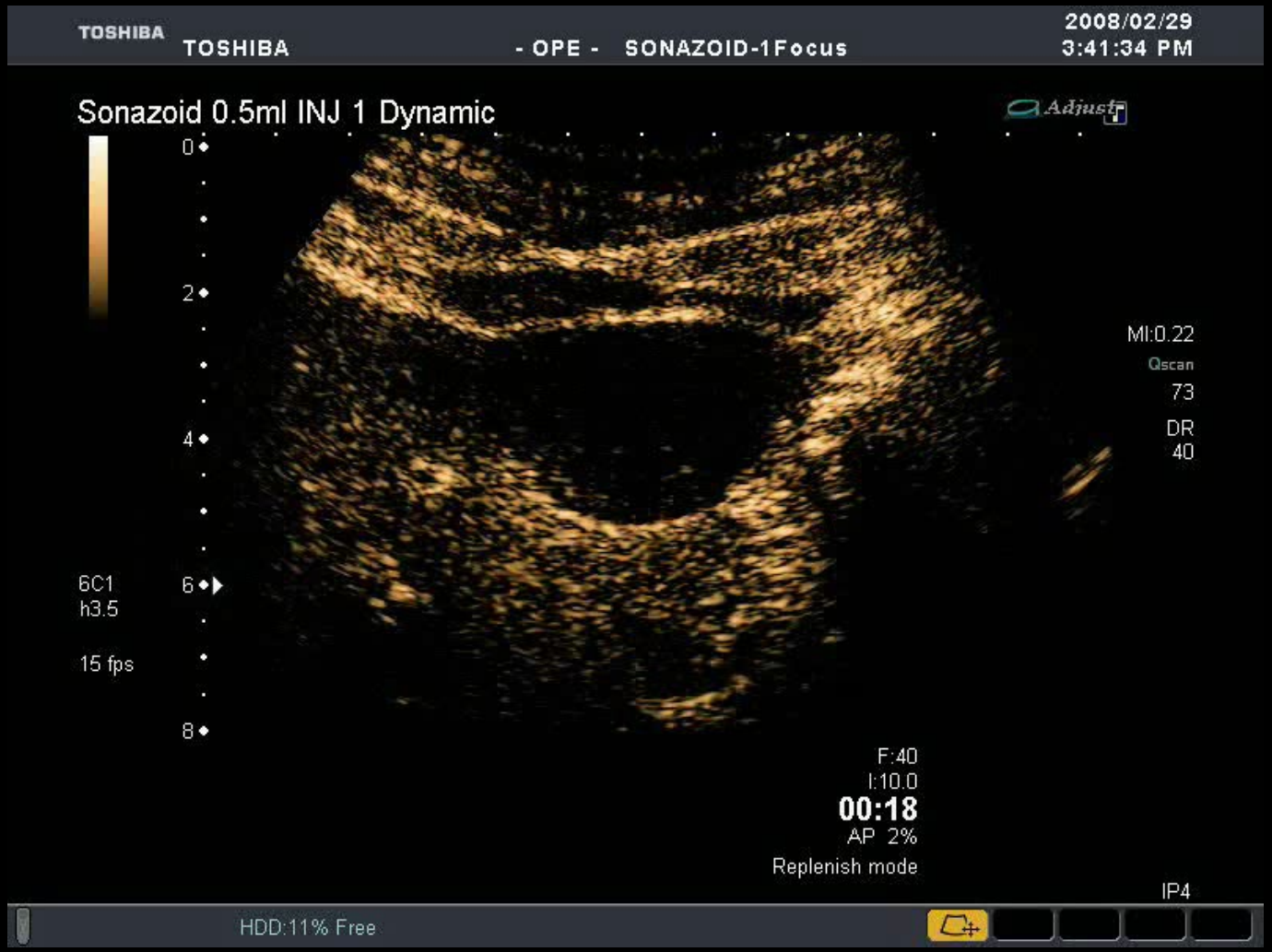
Ultrasound imaging examples with Sonazoid

Contrast-enhanced US: Hemangioma



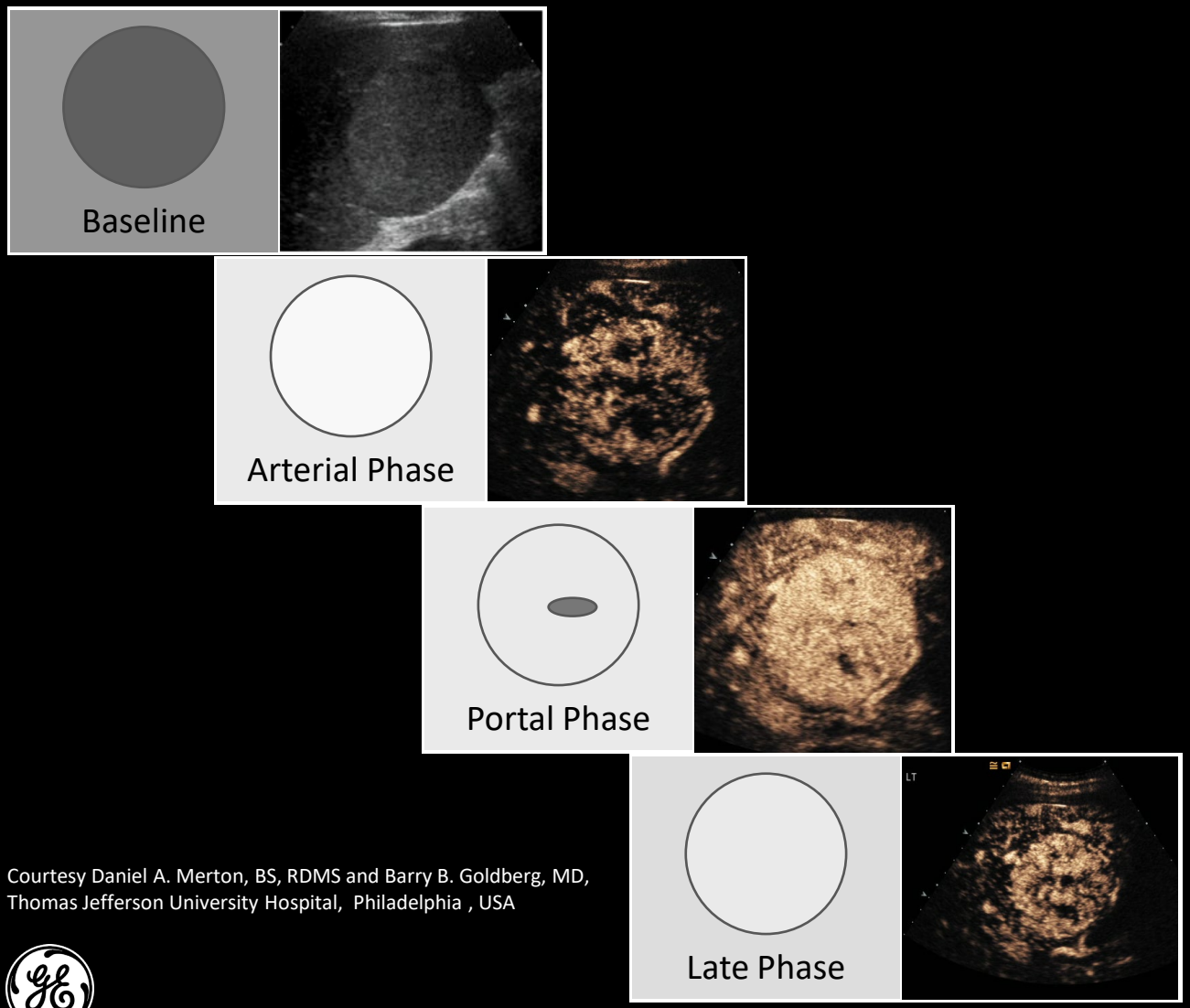
Courtesy Daniel A. Merton, BS, RDMS and Barry B. Goldberg, MD,
Thomas Jefferson University Hospital, Philadelphia , USA

Contrast-enhanced US: Hemangioma



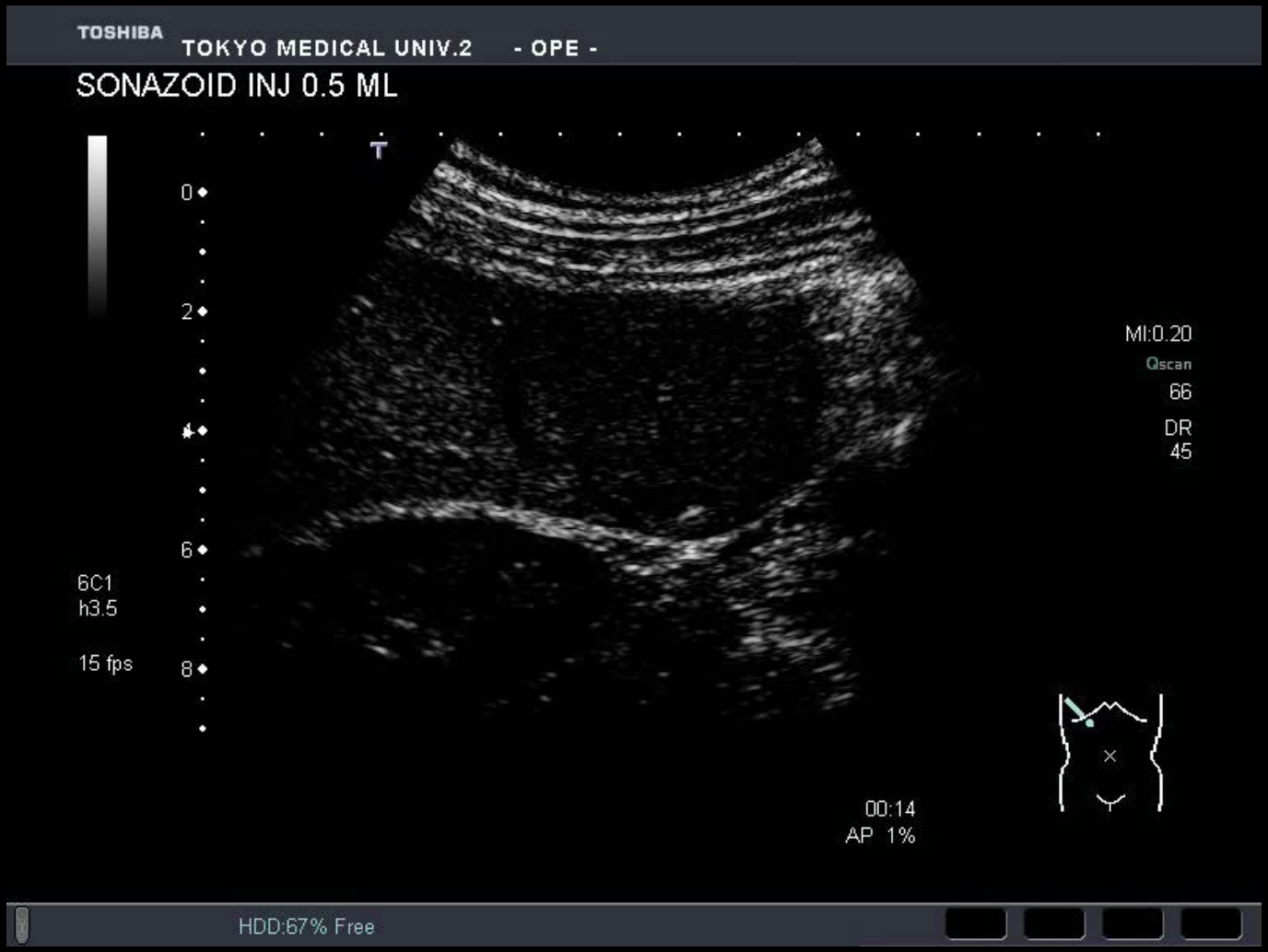
Courtesy Professor Fuminori Moriyasu, Tokyo Medical University, Tokyo, Japan

Contrast-enhanced US: Focal Nodular Hyperplasia



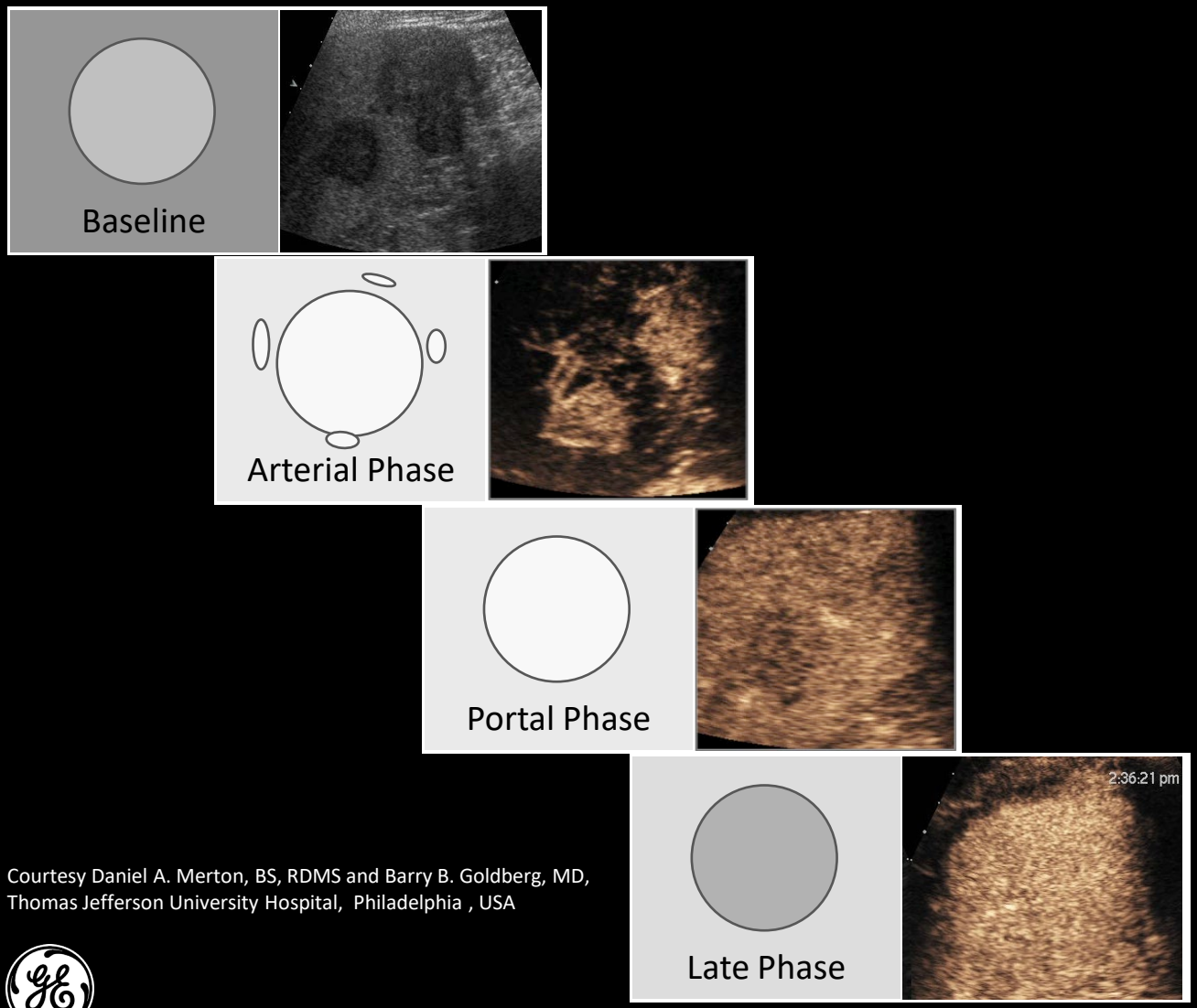
Courtesy Daniel A. Merton, BS, RDMS and Barry B. Goldberg, MD,
Thomas Jefferson University Hospital, Philadelphia , USA

Contrast-enhanced US: Focal Nodular Hyperplasia



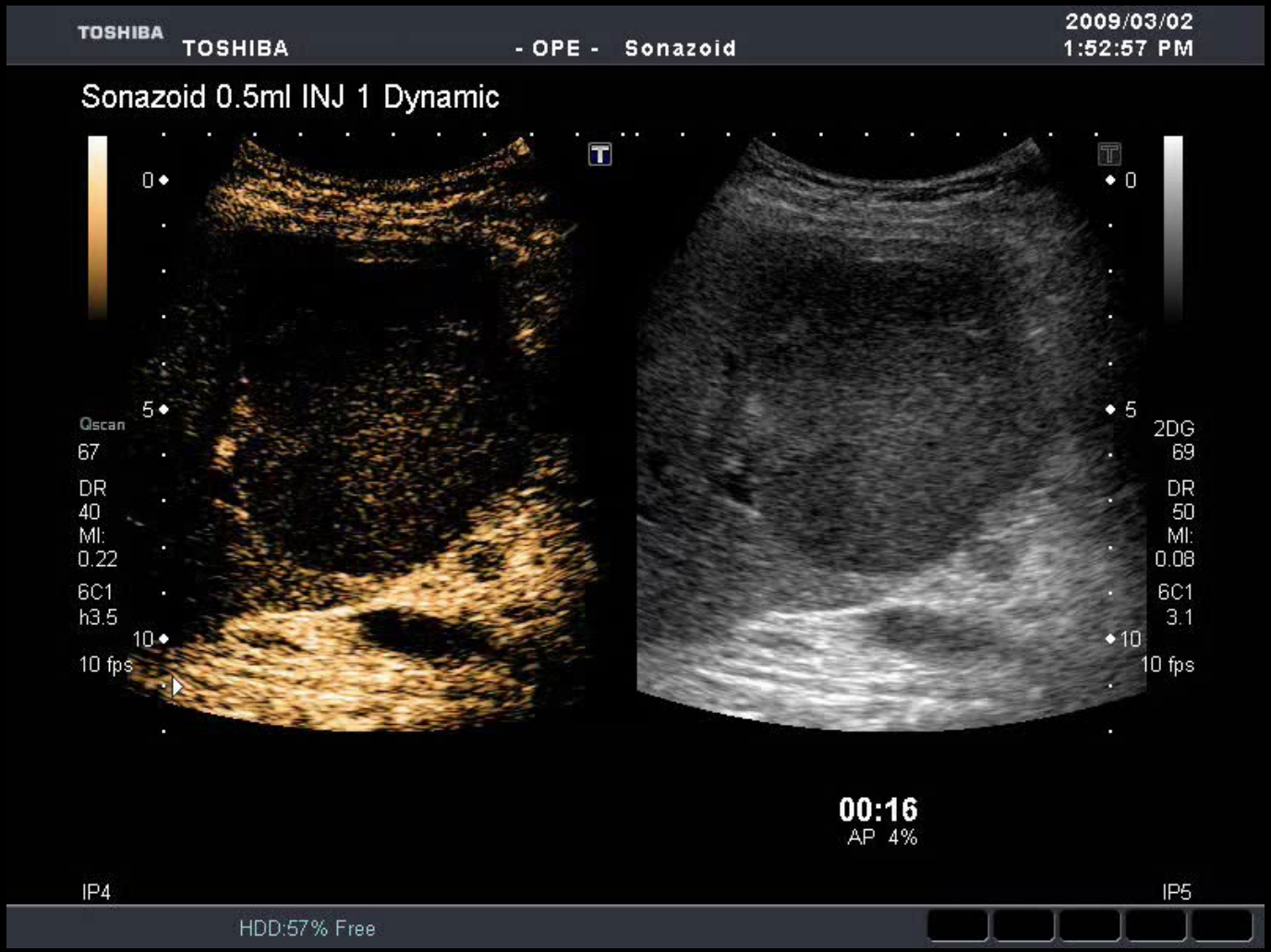
Courtesy Professor Fuminori Moriyasu, Tokyo Medical University, Tokyo, Japan

Contrast-enhanced US: Hepatocellular carcinoma



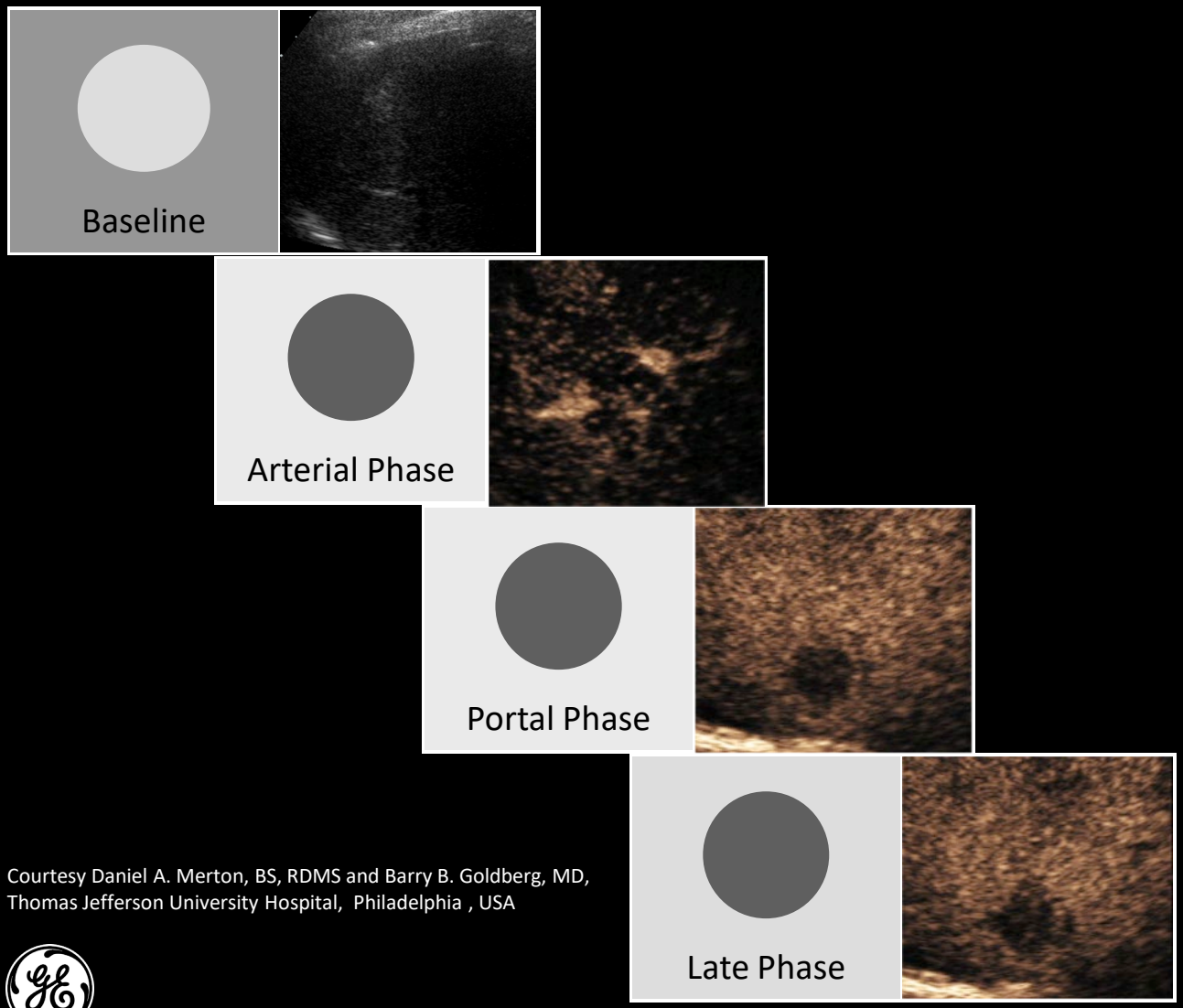
Courtesy Daniel A. Merton, BS, RDMS and Barry B. Goldberg, MD,
Thomas Jefferson University Hospital, Philadelphia , USA

Contrast-enhanced US: Hepatocellular carcinoma



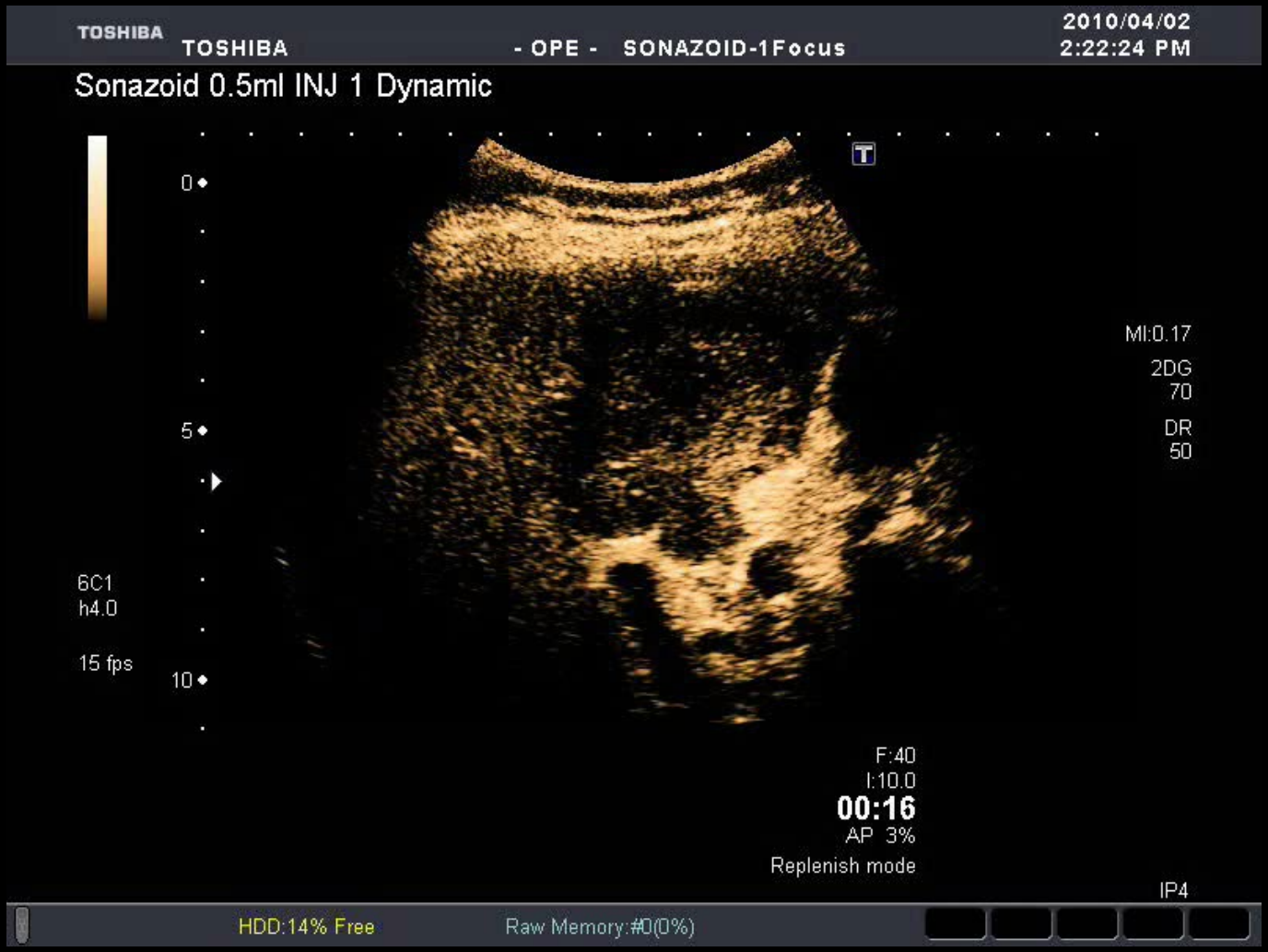
Courtesy Professor Fuminori Moriyasu, Tokyo Medical University, Tokyo, Japan

Contrast-enhanced US: Liver metastasis



Courtesy Daniel A. Merton, BS, RDMS and Barry B. Goldberg, MD,
Thomas Jefferson University Hospital, Philadelphia , USA

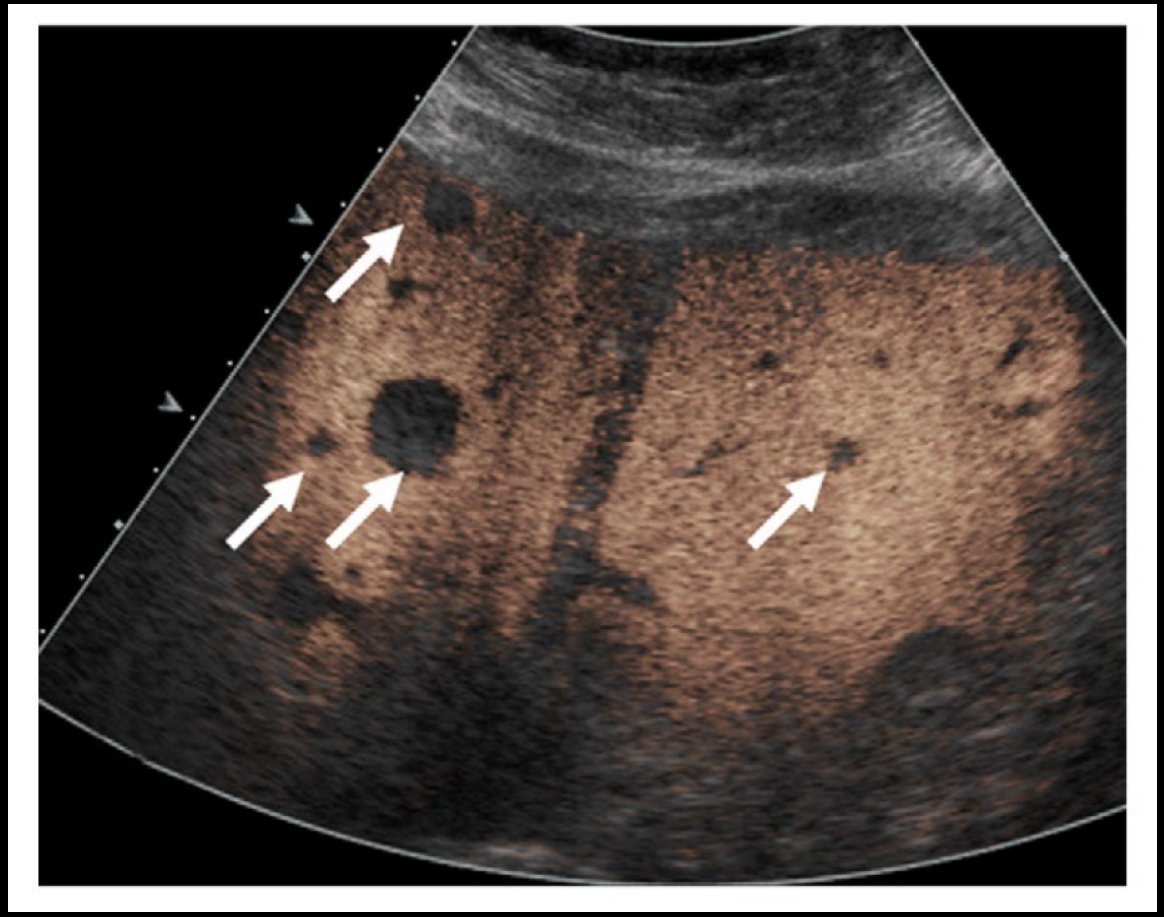
Contrast-enhanced US: Liver metastasis



Courtesy Professor Fuminori Moriyasu, Tokyo Medical University, Tokyo, Japan

Detection of focal liver lesions in the late phase (Kupffer-phase) ≥10 min after injection

In this patient with metastatic pancreatic cancer, several lesions of varying size (some <1 cm) are clearly visible in this late-phase image (~10 min after injection of Sonazoid)[1]



Reference and image courtesy:
1. Edey AJ *et al*. Clinical Radiology 2008; 63: 1112-20.

CHAPTER 6

Efficacy

Clinical trials performed with Sonazoid

The need for contrast agents in liver US was clearly demonstrated in two SonoVue trials

	Off-site reader	Ultrasound type	Sensitivity (%)	Specificity (%)	Accuracy (%)
Leen *et al*, 2006[1]	A	SonoVue	95.4	83.7	91.2
		unenhanced	42.5	30.6	38.2
		SonoVue – unenhanced	52.9	53.1	53.0
	B	SonoVue	90.8	89.8	90.4
		unenhanced	59.8	32.0	41.2
		SonoVue – unenhanced	31.0	57.8	49.2
Dai *et al*, 2007[2]	1	SonoVue	92.5	78.4	87.2
		unenhanced	53.8	22.1	41.9
		SonoVue – unenhanced	38.7	56.3	45.3
	2	SonoVue	88.7	86.5	87.9
		unenhanced	42.5	23.1	35.2
		SonoVue – unenhanced	46.2	63.4	52.7

In these 2 trials there was a good mix of malignant and benign cases. Across the 4 blinded readers:

- Sensitivity improved from 50% to 92%
- Specificity improved from 27% to 85%
- Accuracy improved from 39% to 89%

References:
1. Leen E *et al*. Am J Roentgenology 2006; 186: 1551–9.
2. Dai Y *et al*. Investigative Radiology 2007; 42: 596-603.

Clinical development program with Sonazoid for market authorisation in Norway[1]

Clinical Development Phase	Study title	No. of subjects enrolled
Phase 1	Healthy volunteers	40
Phase 1	Clinical pharmacology study: Single blind, 3-group, 2-period crossover comaprison in healthy adult subjects	27
Phase 2	Dose comparison study in patients with focal hepatic lesions	170 (evaluated for vascular imaging n=165; Kupffer imaging n=163)
Phase 3	Confirmatory study in patients with focal hepatic lesions by comparison of ultrasound before and after contrast enhancement with Sonazoid	196 (evaluated for vascular imaging n=190; Kupffer imaging n=191)

Reference: 1. Data on file, GE Healthcare

Pivotal study for the liver indication[1]

Phase 3 Efficacy

Efficacy of Perflubutane Microbubble–Enhanced Ultrasound in the Characterization and Detection of Focal Liver Lesions: Phase 3 Multicenter Clinical Trial

OBJECTIVE. The purpose of this study was to assess the efficacy and safety of contrast-enhanced ultrasound performed with perflubutane microbubbles in comparison with unenhanced ultrasound and dynamic CT in the characterization of focal liver lesions during the vascular phase of imaging and in the detection of lesions during the Kupffer phase.

SUBJECTS AND METHODS. A total of 196 patients were enrolled at 15 centers in Japan. Vascular phase images were obtained before contrast injection until 1 minute after injection. Kupffer phase images were obtained 10 minutes after injection. Dual-phase CT was performed as determined by standard clinical practice at each center. Unenhanced ultrasound, contrast-enhanced ultrasound, and CT images were read by blinded reviewers, and the results they reached regarding characterization and detection were compared with reference standard findings made by onsite investigators. The safety observation period was 72 hours after contrast administration.

RESULTS. Among the 190 patients included in the characterization analysis, the accuracy of contrast-enhanced ultrasound (88.9%) was significantly greater than that of unenhanced ultrasound (68.4%) and dynamic CT (80.5%) ($p < 0.001$ and $p = 0.008$). Among the 191 patients in the detection analysis, the efficacy of contrast-enhanced ultrasound in detection of lesions was significantly higher than that of unenhanced ultrasound and dynamic CT ($p < 0.001$ and $p = 0.008$), predominantly because more metastatic lesions were detected (both $p < 0.001$). In particular, contrast-enhanced ultrasound was superior to dynamic CT in the detection of metastatic lesions measuring 1 cm or smaller. The incidence of adverse events was 49.2% and that of adverse drug reactions was 10.4%. All adverse drug reactions were mild.

CONCLUSION. Compared with unenhanced ultrasound and dynamic CT, contrast-enhanced ultrasound with perflubutane microbubbles improved diagnostic efficacy in both characterization and detection of focal liver lesions with no serious adverse drug reactions.

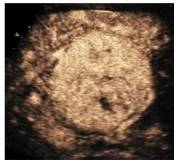
Reference: 1. Moriyasu & Itoh. Am J Roentgenology 2009; 193: 86-95.

Sonazoid and Focal Liver Lesions (FLLs)[1]

Japanese phase 3 study in 190 subjects (164 malignant & 26 benign cases)

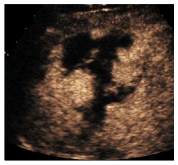
Without Sonazoid / With Sonazoid:

FNH benign



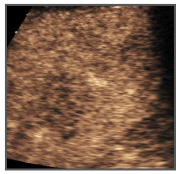
- 68.4% correct specific diagnoses
- 88.9% correct specific diagnoses (p<0.001*)

HAEM benign



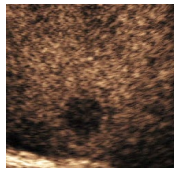
- 89.0% malignant lesions correct (sensitivity)
- 98.8% malignant lesions correct (p<0.001*)

HCC malignant



- 69.2% benign lesions correct (specificity)
- 88.5% benign lesions correct (p=0.096*)

MET malignant



- 86.3% benign/malignant lesions correct (accuracy)
- 97.4% benign/malignant lesions correct (p<0.001*)

Courtesy Daniel A. Merton, BS, RDMS and Barry B. Goldberg, MD, Thomas Jefferson University Hospital, Philadelphia, USA

Reference: 1. Moriyasu & Itoh. Am J Roentgenology 2009; 193: 86-95.

***McNemar test**
FNH: Focal Nodular Hyperplasia
HAEM: Hemangioma
HCC: Hepatocellular Carcinoma
MET: Metastasis

Detection of FLLs in the late (Kupffer) phase[1] –

Results from the Japanese phase 3 study

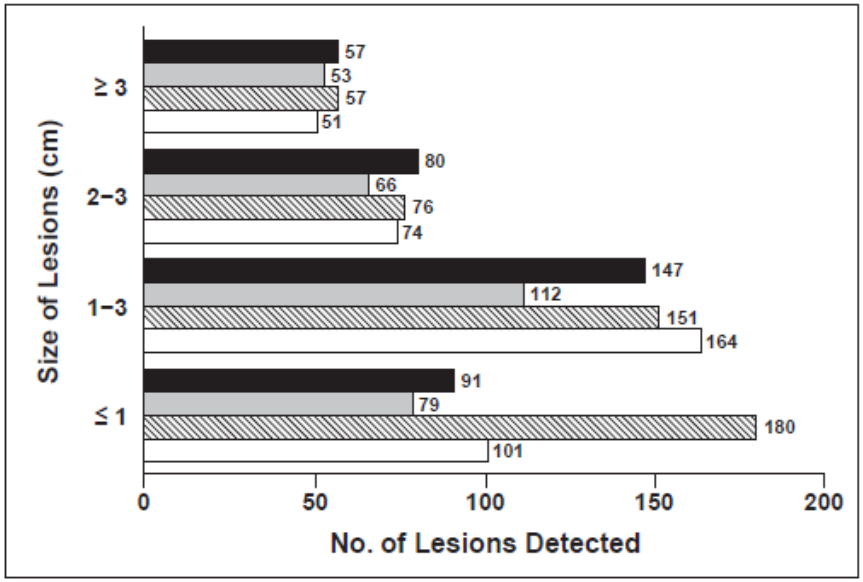


Fig. 6—Graph shows number of lesions classified according to lesion size detected by blinded reviewers using unenhanced ultrasound (*gray*), contrast-enhanced ultrasound (CEUS) (*striped*), and dynamic CT (*white*) and by onsite investigators using reference standard (*black*). Wilcoxon's signed rank test for lesions 1 cm or smaller, CEUS vs dynamic CT, $p = 0.008$; CEUS vs unenhanced ultrasound, $p < 0.001$; CEUS vs reference standard, $p = 0.001$.

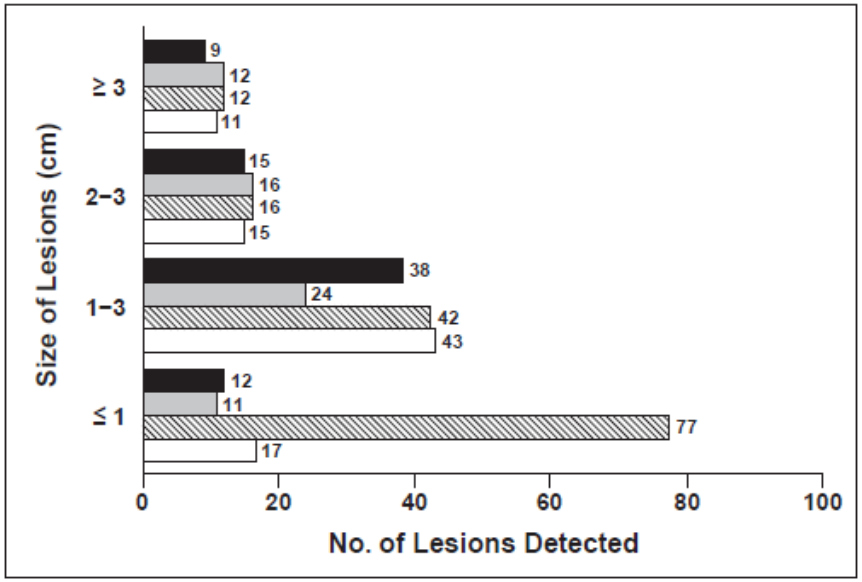


Fig. 7—Graph shows number of metastatic lesions classified according to lesion size detected by blinded reviewers using unenhanced ultrasound (*gray*), contrast-enhanced ultrasound (CEUS) (*striped*), and dynamic CT (*white*) and by onsite investigators using reference standard (*black*). Wilcoxon's signed rank test for lesions 1 cm or smaller, CEUS vs dynamic CT, $p < 0.001$; CEUS vs unenhanced ultrasound, $p < 0.001$; CEUS vs reference standard, $p < 0.001$.

CEUS detects significantly more small lesions, especially metastases, than unenhanced US, dynamic CECT & the on-site reference standard. (Note: not all lesions were confirmed by follow up)[1]

Adapted from reference: 1. Moriyasu & Itoh. Am J Roentgenology 2009; 193: 86-95.

FLLs = Focal Liver Lesions

Comparison CEUS, CT and MRI[1]
Study design

A Prospective Assessment of the Diagnostic Value of Contrast-Enhanced Ultrasound, Dynamic Computed Tomography and Magnetic Resonance Imaging for Patients with Small Liver Tumors[1]

A prospective study assessing the diagnostic value of contrast-enhanced ultrasound (CEUS) using long Kupffer phase enhancement for adults with liver tumor size of less than 3 cm. Performance comparisons conducted with dynamic computed tomography (CT) and magnetic resonance imaging (MRI).

Sixty-six adult patients suspected of having liver tumors smaller than 3 cm underwent CEUS, dynamic CT, and MRI examinations independently. Subsequent tumor biopsies were used to verify the diagnostic performance of the three imaging modalities.

1. Chih-Yang Hsiao, Po-Da Chen, and Kai-Wen Huang. J. Clin. Med. 2019, 8, 1353; doi:10.3390/jcm8091353

Comparison CEUS, CT and MRI[1] Results

Table 3. Performance of CEUS, MRI, and CT in the diagnosis of liver tumors smaller than 3 cm.

	HCC					Liver Metastasis					All Malignancy				
	Sen	Spe	DOR (95% CI)	PPV	NPV	Sen	Spe	DOR (95% CI)	PPV	NPV	Sen	Spe	DOR (95% CI)	PPV	NPV
CEUS	87.8	88	52.8 (11.4–243)	92.3	81.5	80	98	200 (19.1–2095)	92.3	94.3	92.9	100	260 (12.7–5310)	100	71.4
MRI	90.2	76	29.29 (7.36–116)	86	82.6	60	94.1	24 (5.05–114)	75	88.9	85.7	30	2.57 (0.55–12.1)	87.3	27.3
CT	82.9	80	19.43 (5.44–69.4	87.2	74.1	66.7	94.1	32 (6.56–156)	76.9	90.6	83.9	50	5.22 (1.25–21.8)	90.4	35.7

CEUS, contrast-enhanced ultrasound; CI, confidence interval; CT, computed tomography; DOR, diagnostic odds ratio; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spe, specificity.

For HCC, CEUS had the best PPV (92.3%) . For all-malignancy (combined HCC and metastatic tumor as a single diagnosis), CEUS had the best PPV and NPV.

1. Chih-Yang Hsiao, Po-Da Chen, and Kai-Wen Huang. J. Clin. Med. 2019, 8, 1353; doi:10.3390/jcm8091353

Comparison CEUS, CT and MRI[1] Conclusions

- Study results indicate that CEUS is superior to dynamic CT and it is essential to obtain a definite diagnosis (including tumor stage) prior to initiating treatment.

1. Chih-Yang Hsiao, Po-Da Chen, and Kai-Wen Huang. J. Clin. Med. 2019, 8, 1353; doi:10.3390/jcm8091353

CHAPTER 7

Ultrasound imaging guidelines

Guidelines Contrast Enhanced Ultrasound (CEUS)

GUIDELINES AND GOOD CLINICAL PRACTICE RECOMMENDATIONS FOR CONTRAST ENHANCED ULTRASOUND (CEUS) IN THE LIVER – UPDATE 2012 A WFUMB-EFSUMB INITIATIVE IN COOPERATION WITH REPRESENTATIVES OF AFSUMB, AIUM, ASUM, FLAUS AND ICUS

Michel Claudon,[1,*] Christoph F. Dietrich,[2,*] Byung Ihn Choi,[3] David O. Cosgrove,[4] Masatoshi Kudo,[5] Christian P. Nolsøe,[6] Fabio Piscaglia,[7] Stephanie R. Wilson,[8] Richard G. Barr,[9] Maria C. Chammas,[10] Nitin G. Chaubal,[11] Min-Hua Chen,[12] Dirk Andre Clevert,[13] Jean Michel Correas,[14] Hong Ding,[15] Flemming Forsberg,[16] J. Brian Fowlkes,[17] Robert N. Gibson,[18] Barry B. Goldberg,[19] Nathalie Lassau,[20] Edward L. S. Leen,[21] Robert F. Mattrey,[22] Fuminori Moriyasu,[23] Luigi Solbiati,[24] Hans-Peter Weskott,[25] and Hui-Xiong Xu[26]

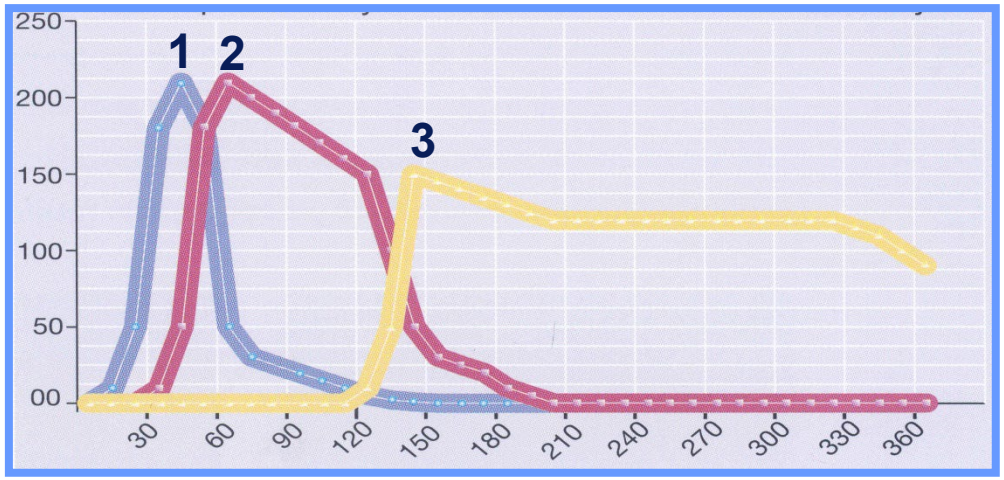
Interpretation of imaging results

- Guidelines have been developed to help provide uniformity in performing and interpreting contrast-enhanced exams for liver lesion characterization
- The latest guidelines were published in Ultrasound in Med & Biol 2013; 39: 187-201, and also online in 2012 in Ultraschall in Med

Guidelines for the use of Contrast Enhanced Ultrasound in the Liver[1]

Characterization of focal liver lesions

- Dual blood supply to liver (hepatic artery and portal vein)
- 3 overlapping vascular phases can be identified with CEUS



1) Arterial phase: 10-35 seconds (degree and pattern of vascularity)
2) Portal-venous: 30-120 seconds (information on wash-out)
3) Late phase: >120 seconds (sinusoid pooling or Kupffer cell uptake)

Reference: 1. WFUMB-EFSUMB Guidelines 2012. Med & Biol 2013; 39: 187-201. http://dx.doi.org/10.1016/j.ultrasmedbio.2012.09.002 Last accessed on 02/2020

Guidelines for the use of Contrast Enhanced Ultrasound in the Liver

The guidelines define the vascular phases

Table 1. Vascular phases in CEUS of the liver (visualization postinjection time)

Phase	Start (s)	End (s)
Arterial	10–20	30–45
Portal venous (PV)	30–45	120
Late	>120	Bubble disappearance (approx. 4–6 min)

The portal and late phases start at the end of the preceding one. Individual hemodynamic and other factors (*e.g.*, site of injection) may influence their time of onset.

However, it should be noted that ”bubble disappearance” does not apply for Sonazoid[1]

Reference: 1. WFUMB-EFSUMB Guidelines 2012. Med & Biol 2013; 39: 187-201. http://dx.doi.org/10.1016/j.ultrasmedbio.2012.09.002 Last accessed on 02/2020

Guidelines for the use of Contrast Enhanced Ultrasound in the Liver[1]

The guidelines give specific information on enhancement patterns of Focal Liver Lesions (FLLs) in late-phase (Kupffer-phase) imaging with Sonazoid

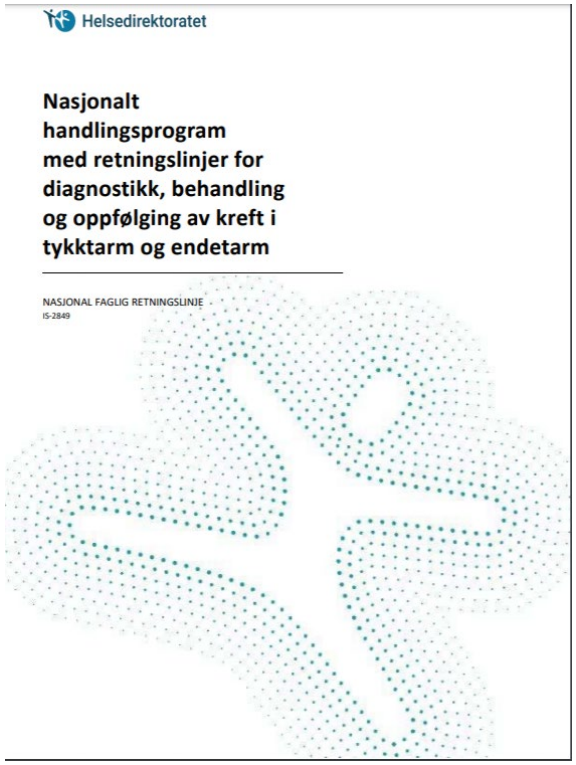
Table 4. Enhancement patterns of focal liver lesions in liver cirrhosis during the postvascular phase (Kupffer phase) with Sonazoid®

Lesion	Post-vascular phase with Sonazoid® (Kupffer phase)
Cyst	Nonenhancing
Hemangioma	Nonenhancing
FNH	Iso to hyperenhancing
Regenerative nodule	
Typical features (but not diagnostic)	Isoenhancing
Additional features (but not diagnostic)	Slightly hypo- or hyperenhancing
Dysplastic nodule	Isoenhancing
HCC	
Typical features	Nonenhancing or hypoenhancing
Additional features	Isoenhancing (well differentiated HCC)
Cholangiocarcinoma	
Typical features	Nonenhancing or hypoenhancing
Additional features	Not reported
Metastasis	
Typical features	Nonenhancing or hypoenhancing
Additional features	Not reported

The arterial and portal venous phases are the same as for other agents. Cholangiocarcinoma may mimic metastasis and poorly differentiated HCC. Metastasis may mimic cholangiocarcinoma and poorly differentiated HCC.

Reference: 1. WFUMB-EFSUMB Guidelines 2012. Med & Biol 2013; 39: 187-201. http://dx.doi.org/10.1016/j.ultrasmedbio.2012.09.002 Last accessed on 02/2020

National guidelines in Norway[1]



Tabell 1. Anbefalt kontrollopplegg for pasienter behandlet med kurativ intensjon for tykktarmskreft, der kurativ reseksjon av residiv/metastaser kan bli aktuelt.

Måneder postop.	1 [1]	6	12	18	24	30	36	48	60
CEA	•	•	•	•	•	•	•	•	•
CT-lever*/ CT-abdomen**		•[2]							•
UL-lever med kontrast (CEUS) [2]			•	•	•	•	•	•	
Lavdose CT-thorax			•		•		•	•	•
Tykktarmsundersøkelse [3]									•

Tabell 2. Anbefalt kontrollopplegg for pasienter behandlet med kurativ intensjon for endetarmskreft, der kurativ reseksjon av residiv/metastaser kan bli aktuelt.

Måneder postop.	1 [1]	6	12	18	24	30	36	48	60
CEA	•	•	•	•	•	•	•	•	•
CT-lever* / CT-abdomen bekken** [2]		•							•
UL-lever med kontrast (CEUS) [2]			•	•	•	•	•	•	
Lavdose CT-thorax			•		•		•	•	•
Tykktarmsundersøkelse [4]									•
Undersøkelse av rektum/perineum og vurdering av plager relatert til funksjon [3,5]		•	•	•	•	•	•	•	•

Reference:

1. Helsedirektoriatet, Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av tykk- og endetarmskreft. Norway 09/2019, ISBN 978-82-8081-605-4

CHAPTER 8

Safety Profile

Special warnings and precautions for use[1]

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.

Reference: 1. Sonazoid SmPC Norway 05/2019.

Safety experience with Sonazoid[1]

Adverse reactions to Sonazoid are usually non-serious. Reported adverse reactions following the use of Sonazoid were mild to moderate in severity 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.

Reference: 1. Sonazoid SmPC Norway 05/2019.

Prescribing information

SONAZOID 8 mikroliter per ml pulver og væske til injeksjonsvæske, dispersjon
(Vennligst konsulter fullstendig preparatomtale [SPC] før bruk)

LEGEMIDDELFORM Pulver og væske til injeksjonsvæske, dispersjon

VIRKESTOFF OG STYRKE Perfluorobutan mikrobobler 8 mikroliter per ml.

INDIKASJONER Dette legemidlet er kun til bruk ved diagnostiske formål. Sonazoid er et ultralydkontrastmiddel for bruk i vaskulær fase og Kupffer-fase for ultrasonisk avbildning av fokale leverlesjoner.

DOSERING OG ADMINISTRASJONSMÅTE Dette legemidlet skal kun gis av lege eller annet kvalifisert helsepersonell. Den anbefalte dosen for en voksen er opp til et hetteglass av produktet inneholdende 16 mikroliter av perfluorobutan (PFB) mikrobobler (MB) suspendert i **2 ml** av den medfølgende væsken for rekonstituering for å lage en 0,015 ml/kg dispersjon. Det rekonstituerte produktet er kun for intravenøs bruk. Den anbefalte dosen er 0,12 mikroliter PFB mikrobobler/kg kroppsvekt. Se fullstendig SPC for anbefalt vektbasert dosering og instruksjoner for tilberedning og bruk. Ultralyd bildeopptak må utføres under injeksjon av Sonazoid da optimal kontrastvirkning oppnås umiddelbart etter administrasjon. Sikkerheten ved bruk av dette produktet er ikke fastslått hos barn (ingen data er tilgjengelig).

KONTRAINDIKASJONER Overfølsomhet overfor virkestoffet eller noen av hjelpestoffene.

ADVARSLER OG FORSIKTIGHETSREGLER Muligheten for overfølsomhet, inkludert alvorlig, livstruende anafylaktoid reaksjon / anafylaktoid sjokk bør alltid vurderes. Avansert livredningsutstyr bør være lett tilgjengelig. Sonazoid inneholder et kyllingegg-avledet surfaktant (hydrogenert fosfatidylserinnatrium fra egg, H-EPSNa). Hos pasienter som tidligere har hatt allergi mot egg eller eggprodukter, skal Sonazoid bare brukes hvis fordelen klart oppveier den potensielle risikoen. Forsiktighet bør utvises hos pasienter med høyre til venstre arteriovenøs hjerte-eller lunge shunt, da Sonazoid entrer sirkulasjonen direkte uten å passere gjennom lungene. Forsiktighet bør utvises ved bruk av ultralyd kontrastmidler hos pasienter med ustabile hjertetilstander eller alvorlig koronar arteriell sykdom. Sonazoid bør administreres med forsiktighet hos pasienter med alvorlig lungesykdom da det utskilles hovedsakelig via lungene. Ultralyd med Sonazoid kan bli negativt påvirket av overdreven intraabdominal gass etter laparoskopi, perorale bariumundersøkelser med bruk av et skummingsmiddel eller andre gastrointestinale undersøkelser.

INTERAKSJON MED ANDRE LEGEMIDLER OG ANDRE FORMER FOR INTERAKSJON
Interaksjonsstudier er ikke utført hos mennesker. En interaksjonsstudie utført in vitro viste ingen effekter av Sonazoid på de mest vanlige anti-trombotiske legemidler, ved bruk av Sonazoid i konsentrasjoner som tilsvarer anbefalt klinisk dose.

FERTILITET, GRAVIDITET OG AMMING Sikkerheten ved bruk av Sonazoid under graviditet hos mennesker er ikke fastslått. Dyrestudier indikerer ikke reproduksjonstoksisitet. Sonazoid bør ikke brukes under graviditet hvis ikke fordelen oppveier risikoen. Det er ikke kjent om Sonazoid utskilles i morsmelk. Det er ikke klarlagt om barn som ammes kan påvirkes. Forsiktighet bør derfor utvises når Sonazoid administreres til ammende kvinner.

BIVIRKNINGER Bivirkninger etter bruk av Sonazoid er vanligvis ikke alvorlige. Rapporterte bivirkninger etter bruk av Sonazoid var milde til moderate med påfølgende full restitusjon. De hyppigst rapporterte bivirkningene var hodepine, diaré, kvalme, oppkast, magesmerter, forbigående endret smak og feber. Tilfeller av hypersensitivitetsreaksjoner er rapportert (mindre vanlig), anafylaktoid reaksjon og anafylaktoid sjokk har vært rapportert. Følgende bivirkninger er kjent ved bruk av Sonazoid: *Forstyrrelser i immunsystemet:* Hypersensitivitet, inkludert mild allergisk reaksjon, konjunktivitt, rhinitt, utslett, pruritus (mindre vanlig), anafylaktoid sjokk, anafylaktoid reaksjon (frekvens ikke kjent). *Nevrologiske sykdommer:* Hodepine, svimmelhet, smaksforstyrrelser (mindre vanlig). *Gastrointestinale sykdommer:* Diaré, oppkast, kvalme, magesmerter (mindre vanlig). *Karsykdommer:* Rødming (mindre vanlig). *Generelle lidelser og reaksjoner på injeksjonsstedet:* Smerter på injeksjonsstedet, reaksjon på injeksjonsstedet, feber (mindre vanlig). Resultater fra kliniske studier indikerer ingen aldersrelatert økning i forekomsten av uønskede hendelser eller bivirkninger hos eldre pasienter.

Melding av mistenkte bivirkninger etter godkjenning av legemidlet er viktig. Det gjør det mulig å overvåke forholdet mellom nytte og risiko for legemidlet kontinuerlig. Helsepersonell oppfordres til å melde enhver mistenkt bivirkning. Dette gjøres via meldeskjema som finnes på nettsiden til Statens legemiddelverk: www.legemiddelverket.no/meldeskjema.

INSTRUKSJON VEDRØRENDE BRUK OG HÅNDTERING Undersøk legemidlet før bruk for å sikre at beholderen og forseglingen ikke er skadet. Hetteglasset er kun ment for engangsbruk. Ikke anvendt legemiddel samt avfall bør destrueres i overensstemmelse med lokale krav. *Forberedelse:* Etter å ha injisert sterilt vann fra medfølgende ampulle inn i hetteglasset og tilberedt dispersjonen, skal alltid den medfølgende opptrekkskanylen brukes til å trekke produktet opp i sprøyten. Når produktet trekkes opp i sprøyten og injiseres tilbake i hetteglasset, skal dette gjøres sakte for å unngå overdreven dekomprimering/kompresjon. Bruk av et annet rekonstitueringsmiddel enn den medfølgende væsken for rekonstituering kan forårsake dannelse av aggregater. Åpne medfølgende ampulle for rekonstituering: Tørk av ampullen med en etanol- desinfiserende klut før åpning for å unngå kontaminering. Dra 2 ml av medfølgende sterilt vann opp i en tom sprøyte. Sett medfølgende opptrekkskanyle inn i hetteglasset (frysetørket doseringsform).

Prescribing information

Fest sprøyten som inneholder **2 ml** sterilt vann til opptrekkskanylen, injiser sterilt vann inn i hetteglasset, og rist deretter umiddelbart i ett minutt mens sprøyten fremdeles er festet. Noe vann vil forbli i dødvolumet inne i opptrekkskanylen, så dra hele volumet av dispersjonen (2 ml) opp i sprøyten én gang og injiser deretter alt tilbake i hetteglasset. Fest sprøyten for injeksjon av dispersjonen i opptrekkskanylen og trekk den ønskede dose opp i sprøyten. *Administrering:* Bruk en kanyle med en størrelse på minst 22 G. Separasjon av dispersjonen kan forekomme ved henstand, så rist produktet umiddelbart før administrering for å sikre homogent innhold. Tilførselsvei bør normalt skylles med en liten mengde av isotonisk natriumkloridoppløsning (ISCS) umiddelbart etter administrering av produktet. Etter åpning: Produktglasset er beregnet for engangsbruk, og eventuelt gjenværende produkt må kasseres sammen med opptrekkskanylen etter bruk. Det vises til fullstendig SPC for illustrasjon av tilberedning og opptrekksprosedyre. Oppbevares ved høyst 30°C. Skal ikke fryses. Dispersjonen bør brukes innen 2 timer etter tilberedning.

PAKNING Sonazoid leveres som et sett som inneholder: Et Type I hetteglass som inneholder 16 mikroliter perfluorobutan mikrobobler (frysetørret doseringsform). Hetteglasset er lukket med en gummipropp (lateksfri) og forseglet med en aluminiumskapsel. En ampulle sterilt vann til injeksjon med et lavt innhold av flerverdige kationer. En opptrekkskanyle med 0,20 mikrometer luftfilter og et 5 mikrometer væskefilter.

GODKJENT UTSALGSPRIS 704,09

RESEPTGRUPPE C.

INNEHAVER AV MARKEDSFØRINGSTILLATELSEN GE Healthcare AS, Postboks 4220 Nydalen, NO-0401 OSLO

MARKEDSFØRINGSTILLATELSESNUMRE 11-8225

Oppdateringsdato Juni 2019 – basert på SPC datert 22.05.2019