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Ultrasound Societies Urge FDA to Remove “Black Box” on Ultrasound Contrast Agents

CHICAGO – (Business Wire) – National and international ultrasound societies are urging the Food and Drug Administration to remove the “black box” from ultrasound contrast agent (UCA) labels.

“UCAs are among the safest diagnostic imaging products available,” according to a Citizen Petition filed by the International Contrast Ultrasound Society (ICUS).

UCAs are used worldwide to enhance diagnostic ultrasound scans, according to the Petition, which cited an extensive body of favorable safety data that was not available in 2007 when the boxed warnings were first mandated by the FDA.

“It is clear to all who work in the field on a daily basis that the black box harms patient care by misrepresenting risk and inappropriately deterring the use of UCAs when they are medically indicated,” said Dr. Steven Feinstein, Co-President of ICUS and Professor of Medicine at Rush University Medical Center in Chicago.

“There is now a strong consensus from across the adult and pediatric medical ultrasound community that ultrasound contrast agents are extremely safe and do not warrant boxed warnings,” he added.

Medical societies supporting the ICUS Petition include the American Institute of Ultrasound in Medicine (AIUM), the World Federation of Ultrasound in Medicine and Biology (WFUMB), the Society of Radiologists in Ultrasound (SRU), the Society of Diagnostic Medical Sonography (SDMS), the Society for Pediatric Radiology (SPR), the American Society of Echocardiography (ASE), and the Liver Imaging Reporting and Data System (LI-RADS) contrast-enhanced ultrasound (CEUS) working group. Numerous individual physicians also submitted letters supporting the ICUS Petition.

“We are disappointed that ‘black box warnings’ are still mandated for ultrasound contrast agents, despite extensive scientific research and practice demonstrating their safety,” according to Dr. Brian Coley, AIUM President, Professor of Medicine and Radiologist-in-Chief at Cincinnati Children’s Hospital.

According to the ICUS Petition, UCAs are injected into a patient’s arm vein during a diagnostic ultrasound scan to help diagnose heart disease, pinpoint and characterize cancers, monitor chronic gastro-intestinal diseases, detect vascular disease, evaluate other serious medical conditions and monitor therapy.

By improving the reliability of real-time ultrasound scans, UCAs often reduce the need for unnecessary downstream tests and related costs, speed up the time to diagnosis and access to appropriate therapy, reduce the length of hospital stays, and improve patient care, outcomes and experiences.

UCAs do not contain radioactive material or dye, present no known risk of kidney or liver damage, and do not require sedation. UCAs are metabolized and expelled from the body, primarily through the lungs, within minutes.

“Our collective experience shows that UCAs are exceedingly safe and beneficial, and they can change patient outcomes and improve patient experiences,” according to a statement submitted by the SRU on behalf of American radiologists with expertise in ultrasound.

The SRU statement added that CEUS is often “equivalent to or superior to CT and MRI, yet it is less expensive, more patient-friendly, more widely available, and completely radiation-free.”

According to the ICUS Petition, a “black box” warning is appropriate only as an indicator of the very highest level risk associated with FDA-approved products, and studies now show “no increased safety signal even among the sickest patients.” The Petition described safety studies undertaken after 2007 at the request of the FDA, as well as other independent studies recently published in peer-reviewed journals.

“The data now clearly and consistently show that UCAs are extremely safe - even in the sickest patients,” according to Dr. Michael Main, a cardiologist at Saint Luke’s Mid America Heart Institute in Kansas City. Main is a Vice President of ICUS and the principal author of recent studies examining the safety of UCAs.

Dr. Richard Barr, a radiologist in Youngstown, Ohio, wrote that his physician group has used CEUS in more than 3,000 patients over more than 10 years, without a single significant adverse event. Barr is also the editor-in-chief of the Journal of Ultrasound in Medicine and stated that he supports the ICUS Petition.

In addition, Barr said that CEUS prevented a large number of biopsies and surgeries, and allowed his group to confirm benign lesions with confidence and detect other lesions at an earlier stage so that appropriate therapy could be provided more quickly. He noted that CEUS is also an important tool for patients who are unable to tolerate contrast CT or MR, such as patients with kidney insufficiency.

CEUS also offers a “huge advantage” for pediatric patients, according to Dr. Kassa Darge, Radiologist-in-Chief at Children’s Hospital of Philadelphia. He said CEUS can reduce or eliminate radiation exposure, avoid sedation or anesthesia, avoid gadolinium contrast deposits -- and ultimately is “much more sensitive or depicts the pathology clearer” in many pediatric ultrasound scans.

Darge said that the “high safety profile” of CEUS in children has now been documented in scientific publications encompassing thousands of children, and there are “no real scientific reasons for having this label.”

Yet because of the black box, some physicians are unduly reluctant to refer patients for CEUS and some patients are apprehensive about receiving UCAs, according to Barr and other experts who weighed in on the Petition.

“The unnecessary presence of a black box results in unfounded fears of utilization of these extremely beneficial agents, and patients are thus exposed to potentially more harmful investigative procedures, or worse, have no information due to uninterpretable, or misinterpreted ultrasound studies, resulting in

missed or wrong diagnoses,” according to Dr. Sharon Mulvagh, Professor of Medicine Emeritus, Mayo Clinic in Rochester, Minnesota and Professor of Medicine, Dalhousie University in Halifax, Canada.

“The Black Box serves no useful purpose,” according to a letter submitted by Dr. Yuko Kono, clinical professor of medicine and radiology at the University of California, San Diego; Dr. Stephanie Wilson, clinical professor of radiology and medicine at the University of Calgary; and Dr. Andrej Lyschchik, associate professor of radiology at Thomas Jefferson University Hospital in Philadelphia. Kono, Wilson and Lyschchik are members and chair of the CEUS LI-RADS Working Group.

According to Wilson, the United States is behind the rest of the world when it comes to using CEUS, which she described as a very patient friendly, extremely reliable and easy to use imaging tool.

“We believe the boxed warning is not warranted and only discourages the use of CEUS,” according to Dr. Beth McCarville and Dr. Peter Strouse, writing on behalf of SPR, the pediatric radiology organization.

According to McCarville and Strouse, a growing body of literature now validates the excellent safety profile of UCAs, which offer a “safe, sedation-free and radiation-free, low-risk method of assessing a variety of conditions in children and should be embraced and supported by pediatric care providers.”

The ICUS Petition notes that the FDA has steadily responded to the mounting evidence of UCA safety and efficacy by downgrading package insert contraindications three times since 2007 and removing a 30-minute monitoring requirement for patients with pulmonary hypertension or unstable cardiopulmonary conditions. More recently, the FDA approved new indications for use in adults and children.

Three UCAs are currently approved for use in the United States -- Definity (Lantheus Medical Imaging), Lumason (Bracco) and Optison (GE Healthcare).

ICUS represents cardiologists, radiologists, and other physicians and imaging professionals in approximately 60 countries.

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ABOUT ICUS:

The International Contrast Ultrasound Society (ICUS) is an international medical society dedicated to advancing the appropriate use of contrast enhanced ultrasound (CEUS) to improve patient care. ICUS members represent diverse specialties such as cardiology, radiology, vascular imaging, gastro-intestinal imaging, oncology, OB-GYN, and hepatology, and include physicians, scientists, and other ultrasound imaging professionals in approximately 60 countries. For more information about ICUS, please visit www.icus-society.org.

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