

January 21, 2000

**URGENT – BACKGROUND RE: MEDICAL DEVICE RECALL & ADVISORY**

SUBJECT: Recall of St. Jude Medical Products With Silzone® Coating

**Products:** All St. Jude Medical Silzone® coated  
prosthetic heart valves and Silzone® coated  
annuloplasty rings  
**Lot Numbers:** All lot numbers

Dear Doctor and other St. Jude Medical Customers:

This letter is a follow-up to the January 21, 2000, recall notification of all products with Silzone® coating.

**I. Reason For Recall**

St. Jude Medical has received information that indicates there is a statistically significant higher rate of paravalvular leak leading to valve explants in patients implanted with St. Jude Medical mechanical heart valves with Silzone® coated sewing cuffs.

Patient safety continues to be St. Jude's primary concern and first priority. St. Jude Medical is therefore initiating a voluntary recall of all unimplanted products incorporating Silzone® coating.

This recall does not involve any St. Jude Medical products without Silzone® coating.

**II. Background**

The Silzone® coating technology is a thin application of elemental silver. St. Jude Medical introduced mechanical valves with Silzone® coating on the sewing cuff for international market releases in July, 1997 and obtained United States FDA approval in March, 1998. These mechanical valves with Silzone® coating are conventional St. Jude Medical mechanical heart valves with the added feature of the Silzone® coating on the valves' sewing cuff.

January 21, 2000

Page 2

The clinical study known as AVERT (the "Study") was designed to determine the effect of the Silzone® coating on the incidence of prosthetic valve endocarditis. The Study is an international, multi-center, randomized clinical trial designed to evaluate the clinical performance of St. Jude Medical mechanical heart valves with Silzone® coating versus conventional St. Jude Medical mechanical heart valves (i.e., those without Silzone® coating). Seventeen sites (7 European, 10 North American) are participating in the trial, which began in July 1998. Study administration is under the direction of the Data Coordinating Center ("DCC") at the University of Pittsburgh's Department of Epidemiology.

Results from the AVERT Study have been periodically reviewed by an independent Data and Safety Monitoring Board ("DSMB") composed of one statistician, one infectious disease expert, one cardiothoracic surgeon, and two cardiologists.

On January 21, 2000, after careful review of the statistical analysis and individual case reports, the DSMB recommended discontinuing patient enrollment in the trial. Although it noted that the total number of relevant events in the Study to date was small, the DSMB determined to suspend patient recruitment into the Study based on indications that there is a higher explant rate due to paravalvular leak for mechanical heart valves with Silzone® coating as compared with conventional (i.e., non-Silzone® coated) St. Jude Medical® mechanical heart valves. In considering the DSMB's decision, St. Jude Medical voluntarily decided to initiate the withdrawal of products with Silzone® coating from the market effective immediately. The randomized nature of the AVERT Study allowed this assessment to be made.

The reported complications resulting in explant in the AVERT Study were detected when patients reported changes in their symptoms. The Study calls for patients to be evaluated via office visit, telephone follow-up or mail survey at discharge, three months, one year and annually thereafter. The AVERT Study did not require unique follow-up diagnostic testing.

Based on our internal investigation, we have concluded that the explants due to paravalvular leak in the AVERT Study are not related to the manufacturing of the valve or the manufacturing of the Silzone® coated sewing cuff. Additional background information on the findings from the AVERT Study is provide din Appendix A.

### **III. Patient Follow-Up**

Led by Dr. Robert Frater, a New York City cardiac surgeon who is Medical Director of St. Jude Medical, St. Jude Medical has a number of observations concerning the follow-up and treatment of patients with a valve or other product with Silzone® coating. First, in reviewing the AVERT data, there appear to be no unique identifying characteristics for the population which experienced paravalvular leakage, with or without suspected endocarditis, and/or the explant population. In addition, instances of paravalvular leakage in the explant patients in the Study did not occur within a specific time period following valve implantation. Consequently, it is not currently possible to identify any specific higher risk subset of patients.

St. Jude Medical is recommending to its clinician customers that the usual admonition to keep scheduled appointments and report all changes in symptoms be emphasize for patients

implanted with valves having the Silzone® coating sewing cuffs. In addition, physicians should follow all normal monitoring and follow-up processes adequate to identify complications or symptoms, including a return or worsening of classic cardiac symptoms or exertional or postural dyspnea or cough, swelling of the ankles or other evidence of fluid retention such as abdominal distention, as well as the less specific symptoms such as fatigue. In a paravalvular leak not caused by infection, the decision for valve explant and replacement is usually made electively.

Diligent normal monitoring of patients with mechanical heart valves should detect the types of paravalvular leak complications observed in the AVERT study.

A summary of more specific follow-up information provided by Dr. Frater is contained in Appendix B.

#### **IV. Other Issues**

DSMB meetings were held on April 13, 1999 and November 1, 1999. These meetings were held in response to concerns that the Silzone® valves showed higher thromboembolic event rates at one U.K. center. At both the April and November, 1999, DSMB meetings, between group differences for all complications, including valve explant and thromboembolic events, were not statistically significant, and the DSMG concluded that it was appropriate to continue patient enrollment in the Study. At the DSMB's January 21, 2000 meeting, thromboembolic events for valves with Silzone® coating on the sewing cuff continued to show no statistically significant differences as compared with the St. Jude Medical conventional mechanical heart valves without Silzone® coating. It has been agreed that the DCC will contact the DSMB if significant changes occur in complication incident rates in the AVERT Study for thromboembolic events and other complications.

#### **V. Continued Follow-up of Already-Enrolled AVERT Patients**

St. Jude Medical will continue to support follow-up of patients already enrolled in the AVERT trial, and will receive continued reports from the AVERT's DSMB. For purposes of further scientific examination as part of the randomized Study, the DSMB recommended at its meeting on January 21 that the AVERT investigators ensure that there is a post implant baseline transthoracic echocardiogram for patients in both arms of the Study (i.e., those with the valves with Silzone coated cuffs and those with the conventional St. Jude Medical mechanical heart valves).

In addition, the DSMB recommended at the January 21 meeting that investigators in the Study monitor any patients (again, those in the Silzone and non-Silzone arm alike) with signs of paravalvular leak for three months with additional echocardiograms to obtain further information about the paravalvular leak phenomenon observed in the Study. St. Jude Medical will work with the DCC and investigators to implement such modifications to the Study protocol.

If information from this continued AVERT review results in any change in the recommended patient follow-up provided here, St. Jude Medical will report this to you and other medical professionals.

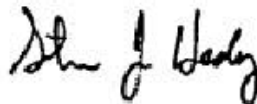
January 21, 2000

Page 4

St. Jude Medical hopes that the above information is helpful to you in understanding the basis for the company's decision to voluntarily initiate a recall of all products with Silzone® coating and its recommendations for follow-up. We apologize for any inconvenience this may cause you.

Sincerely,

**St. Jude Medical, Inc.**

A handwritten signature in black ink, appearing to read "Steven J. Healy". The signature is written in a cursive style with a large initial "S".

Steven J. Healy  
President, St. Jude Medical Heart Valve Division

SJH:  
Enclosure

**Additional Background Concerning AVERT Study Explant Procedures**

Of the 398 patients who received valves with Silzone® coated cuffs in the AVERT Study through January 6, 2000, eight had their valves explanted for paravalvular leak. Through that same date, there has been one explant for paravalvular leak out of the 394 patients in the Study who received the conventional (i.e., non-Silzone® coated) St. Jude Medical® mechanical heart valve.

The eight patients who had Silzone® coated valves explanted all had moderate to severe paravalvular leak, with or without suspected endocarditis. Clinical signs in these patients were generally those associated with valvular regurgitation and heart failure (dyspnea, fatigue, exercise intolerance, etc.).

In an attempt to characterize those patients undergoing re-operation, the AVERT Study DCC performed a comparative assessment of explanted and non-explanted patients. More than 200 variables were compared relating to patient demographic characteristics, medical history, current health status, prior cardiac surgery, operative techniques, concomitant surgical procedures, and operative results/early complications. In addition to the overall analysis, separate analyses were repeated for aortic and mitral valve patients. There were differences between the patients who had explants and those who did not, but, according to the AVERT DCC, the small numbers of the explant group do not allow any conclusions to be drawn. This analysis was unable to detect unique identifying characteristics for the explant population.

The following tabular summary of certain events may be helpful which is based on the present status of the AVERT database:

Event	Silzone-coated cuff		Conventional	
	N=398	%	N=398	%
Paravalvular leak	11	2.76	4	1.02
Explant for paravalvular leak	8	2.01	1	0.25
Paravalvular leak without explant	3	0.75	3	0.76

### Additional Patient Follow-Up Information

#### A. General Comments About Paravalvular Leaks

Since the primary cause of explant in the AVERT Study has been paravalvular leak, further comment on this phenomenon may be helpful. Paravalvular leaks can be divided into two broad categories: infected and uninfected. In the infected cases, it is the infection that is destroying tissue and causing breakdown of the annulus leading to disruption of the suture line. This is a serious situation not only because it produces insufficiency but, more importantly, because it signifies an infection which has no chance for recovery without removal of the valve, and complete eradication of all infected tissue. Any patient with the general signs and symptoms of an infection who has an artificial heart valve in place needs urgent investigation to rule out endocarditis. A new murmur of insufficiency makes the diagnosis of a paravalvular abscess and paravalvular insufficiency extremely likely and increases the urgency for diagnosis and surgery.

In the uninfected case, there clearly has been a failure of the sutures to remain firmly anchored to the tissues. There are several possible causes of this phenomenon and they may occur singly or together. The paravalvular leak need not be very large to produce symptoms. A small leak may produce hemolysis, which is often manageable medically but may not need to be corrected surgically. In addition, a hole with an area of one mm<sup>2</sup> is large enough to produce cardiac symptoms. On the other hand, a small hole of this nature can be well tolerated and may stay the same size for years.

#### B. Specific Comments About Patients who have valves with Silzone® coated cuffs

In general, patients with Silzone® coated valves should be followed in the manner of all patients with heart valve replacements. Their anticoagulation should be managed as usual. They should be instructed to report any change in their symptoms, including a return or worsening of the classic cardiac symptoms of exertional or postural dyspnea or cough, swelling of the ankles or other evidence of fluid retention such as abdominal distention, as well as the less specific symptoms such as fatigue. These symptoms may, of course be produced by other mechanisms such as a chronically failing left ventricle, but whatever the cause, they should be seen when symptoms change, or when symptoms have failed to improve after surgery. Auscultation, followed by transthoracic echocardiography will diagnose most cases of paravalvular leak, with transesophageal echo being used in cases in which the transthoracic images do not provide the answer (as in cases of double valve replacement when acoustic shadows interfere with the imaging).

In the absence of symptoms and with no murmurs of insufficiency, there is no need to obtain an echocardiogram. If a paravalvular leak has been found in an asymptomatic patient, it may be observed with repeat echocardiograms at three to six month intervals until it is established that it is not increasing in size.

As always, if the patient develops a fever or other signs of a suspected infection, he should report this to his or her physician.

**Recall of St. Jude Medical® Mechanical Heart Valve with Silzone® coating  
Patient Questions and Answers**

**I. How do I know if I have a Silzone valve?**

There are several ways to verify if you have a Silzone coated St. Jude Medical heart valve product.

- You can look at the model number on your Patient ID Card. If it is not one of the model numbers referenced in Table 1, you do not have Silzone® coated fabric in heart valve product. Table 1 is listed at the end of this section.
- If you do not have your Patient ID Card, you can call the St. Jude Medical Information Center at 1-800-922-9219 or 651-490-4305 in the U.S.
- If you had an implant before the dates listed in Table 1, you do not have a product with Silzone coating on the sewing cuff. Table 2 lists the dates when Silzone products were approved for use in different parts of the world.

**II. If I do have a valve that incorporates Silzone® coated fabric what should I do?**

To clarify, this recall involves only products on hospital shelves. St. Jude Medical is not recalling any implanted products. We have provided advisory information to physicians regarding implanted valves with Silzone cuffs and we have placed information on our Web site ([www.sjm.com](http://www.sjm.com)).

This is not an emergency situation. This recall involves a complication that can sometimes occur following heart valve replacement. We encourage you to contact your physician.

You are probably on a routine schedule of follow up with your doctor or health care professional. It is important to keep you regularly scheduled follow-up appointments. We urge you to contact your doctor or doctor's office for more information.

We hope this information is helpful in answering your questions. We will continuously update you with relevant information, as it is available.

**Possible Patient Letter**  
(Revise as appropriate)

[Date]

Dear <>:

My records indicate that you have received a St. Jude Medical heart valve product with Silzone® coating on the sewing cuff. I am writing to advise that St. Jude Medical recently voluntarily recalled these heart valves. This recall pertains **only** to Silzone® product that was on hospital shelves, not to valves that have already been implanted.

The voluntary recall is based on a report from a clinical trial that evaluated St. Jude Medical mechanical heart valve products that had Silzone® coating on the sewing cuff. The report indicated that approximately 2 out of 100 patients with Silzone® coating on the cuff of their valves required removal of their valve as a result of a postoperative complication known as paravalvular leak. Paravalvular leak occurs when blood leaks at one or more points around the outside of the implanted valve, between the sewing cuff of the valve and the heart tissue.

The reported paravalvular leak complications that resulted in these valve removals were detected as part of standard patient follow up and were treated by reoperation. If these complications arise, they typically do not present an emergency situation.

I encourage you to continue to keep your normally scheduled follow-up appointments and report any changes in your health to me or to the physician who regularly follows your cardiac status.

If you have any questions, please contact our office.

Sincerely,