OTC Medical Officer's Review

NDA #: 18-683
Drug name (Generic Name): Today Sponge (Nonoxynol-9)
Sponsor: Allendale
Pharmacologic Category: Vaginal Spermicide
Proposed Indication(s): Vaginal Contraceptive
Dosage Form and Route of Administration: Sponge, Vaginal
Submission Date: June 16, 1999
Reviewer Name: Ling Chin
Review Date: April 7, 2000, modified June 12, 2000
CSO/PM Name: Dan Keravich

Safety Review

Materials reviewed:

(1) General Correspondence 6/16/99 from Allendale: Global Safety Summary
(2) Annual Reports submitted for 7/90-6/91 (P-013), 5/93-4/94 (P-016), 5/95-3/96 (P-018), 4/96-2/97 (P-019), 3/97-2/98 (P-020), 3/98-3/99 (P-021)
(3) Consult from Office of Postmarketing Drug Risk Assessment (OPDRA)
(4) CDC Surveillance articles on Toxic Shock Syndrome (TSS)

Background

NDA 18-683 for the Today Sponge was approved as an OTC product in April of 1983. Toxic Shock Syndrome (TSS) cases associated with tampons emerged as a public health hazard in the early 1980's, and cases were also noted with sponge use. Following this occurrence, the Agency recommended changes to the labeling to provide information to consumers about proper use of the sponge, and the risks of TSS. Final Product Labels (FPL) for the Today Sponge were submitted in 1988, 1991, and the sponsor initiated a graphic redesign in 1992.

Over 15 million sponges were sold annually up until 1993 (See Table 1 on page 2). In August of 1993, Whitehall voluntarily ceased production of the sponge presumably due to problems with the manufacturing process. Whitehall further withdrew the sponge from the market in January of 1995. The NDA, however, was not withdrawn. In March of 1999, the NDA was transferred to Allendale Pharmaceuticals. Allendale is currently seeking to manufacture and market the Today Sponge. This review, primarily focussing on TSS, was undertaken to examine the re-introduction of the sponge into the market and to assess if the last approved label (dated 8/26/91) is adequate for the safe and effective use of this product at this time. In addition to a review of the safety update submitted by Allendale and past reports of adverse events (AEs) submitted to the NDA, the Agency's Office of Post-Marketing Drug Risk Assessment searched AERS (Adverse Event Reporting System) for all cases of TSS that were associated with Sponge use.

Safety Considerations

1) Toxic Shock Syndrome

TSS from Centers for Disease Control and Prevention Surveillance[1]

TSS emerged in the early 1980's as an unexplained febrile illness associated with shock, multiorgan dysfunction, and high death rates in healthy young women in the U.S. Initially,

[1] Toxic Shock Syndrome in the United States: Surveillance Update, 1979-1996. Emerging Infectious Diseases; Vol.5 No. 6, 1999, Centers for Disease Control.

reported cases occurred predominantly in young women within 3 days of the beginning or end of menses; these were termed menstrual TSS cases. All other cases were known as non-menstrual TSS cases. Menstrual TSS cases declined from 91% of all TSS cases in 1979-1981 to 71% during 1981-1986, and 59% in 1987-1996. Factors contributing to the decline in menstrual TSS cases included a decrease in tampon absorbency, FDA requirement of standardized labeling, greater awareness of TSS among women, and the proliferation of educational materials for women, including tampon package inserts.

By the time period of 1987-1996, non-menstrual TSS cases averaged 41% of all TSS cases. Of these non-menstrual TSS cases, 18% were reported after surgical procedures, 12% were post-partum or post-abortion, and 23% were nonsurgical cutaneous lesions. Non-menstrual TSS occurred among men and women. Among all female non-menstrual case patients, 12% reported using barrier contraceptives (sponges and diaphragms). When broken out by time period, the proportion was significantly less in 1987-1996 (6%) than in the earlier time period of 1979-1986 (14%).

TSS from manufacturer's reports:

Today Sponge manufacturers reported a total of 106 TSS-like cases to the FDA from 1983 to 1996, from a total of 34 over the first 4 years (1983-1987), then a range of 4 to 14 cases yearly in the ensuing years, with no data reported for 5/94-4/95. See Table 1 below. There were no deaths attributable to TSS in Sponge users in the time periods examined. There were about 90 million sponges sold in the first 4 years, to 20 million in 1988-1989, 18 million in 1990-1991, 15 million in 1992-1993, 9 million in 1993-1994, down to 5,000 in 1995, and zero from 5/95 onwards.

Table 1: TSS-like cases noted in Annual Reports from the sponsor

Sponsors*	Reporting Period	TSS-like Symptoms	# Distributed (millions)
VLI	**6/83-12/87**	34	90.4
W	**1/88-12/88**	14	21.1
W	**1/89-12/89**	11	21.0
W	**1/90-12/90**	6	17.7
W	**7/90-6/91**	7	17.9
**	**5/91-4/92**	4	15.0
**	**5/92-4/93**	12	15.4
W**	**5/93-4/94**	5	9.3
W	**5/94-4/95**	***	.005
W	**5/95-3/96**	13****	0
W	**4/96-2/97**	0	0
W	**3/97-2/98**	0	0
Allendale	**3/98-3/99**		

* **VLI:** Vorhauer Laboratories, Inc.
W: Whitehall Laboratories
Allendale: Allendale Pharmaceuticals

** The figures for the periods of 5/91-4/92 and 5/92-4/93 were taken from the summary table provided in the Annual Report for 5/93-4/94; no Annual Report was submitted for 91-92, 92-93

*** Blank cell spaces indicate that a figure was not provided by the sponsor

**** Figure of 13 reported in 95-96 time period, but date of actual event occurred over several years, during 7/90 to 4/94

TSS from AERS:

A consult was submitted to the OPDRA to review FDA's AERS database for all possible cases of TSS. A summary of the consult is provided below. As of March 6, 2000, there were 5930 reports of all adverse events associated with the Today Sponge. Since prior to November 1997, there was no COSTART term for TSS, a search for TSS cases was done utilizing the preferred terms of "infection", "bacterial infection", "sepsis", "acute circulatory failure", and additional terms such as fever, hypotension, myalgia, influenza like illness, and pharyngitis. A total of 408 reports were selected for manual review, and resulted in the identification of 156 cases of presumed TSS. Of these 156 cases, 89 cases could be deemed possible, probable, or definitive for TSS; i.e. had met at least 3 of CDC's criteria for TSS. While TSS cannot be ruled out in cases that met <3 CDC criteria, there was insufficient clinical information to determine if these cases were truly TSS cases.

Table 2: TSS cases from AERS

CDC Criteria	'83	'84	'85	'86	'87	'88	'89	'90	'91	'92	'93	'94	'95	Total
<3	4	3	8	6	1	8	6	5	6	8	6	5	1	67
3 or more	11	24	3	5	7	8	7	2	9	6	1	6	0	89
Total	15	27	11	11	8	16	13	7	15	14	7	11	1	156

MO Comments: Based on CDC[2] surveillance information, there was a decreasing trend in the number of TSS cases overall, and non-menstrual TSS cases in diaphragm and sponge users over time from 1979 to 1996. There was a decrease in the number of sponges sold from 1983 to 1995, but a steady decrease in number of TSS cases reported (via Annual Reports) to FDA's Spontaneous Reporting System (SRS) from 1983 to 1995 was not seen. It should be noted, however, that a trend analysis of TSS cases could not be performed on this data. There were gaps in the data for certain years. Furthermore, there were errors in the assignment of cases to specific reporting time periods, since not all the cases were recorded in the time period during which they occurred. (The date of the event, the date the report was received by the sponsor, and the date the report was submitted to FDA could all have occurred over different years.) In Table 2, TSS cases retrieved from AERS were summarized by the year of event occurrence. Again, despite a decrease in the numbers of sponges distributed beginning in 1991 (See Table 1), and more drastically in 1993 and 1994, the corresponding decrease in number of TSS cases in AERS was not observed.

Overall, there were more cases found in the AERS database (156) than reported by sponsors (106).[3] However, the AERS database does include voluntary reports submitted directly to FDA, and these reports would not have been available to the sponsor unless the reporter also

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[2] The CDC Surveillance Case Definition (1981) of TSS is as follows:

1. Fever
2. Hypotension
3. Rash
4. Desquamation
5. Abnormalities in 3 or more organ systems

A definite case would have met all of the 5 clinical criteria established. A probable case would have met 4 of the 5 criteria. However, since information on desquamation was often missing, CDC decided to include all TSS reports meeting either definition.

[3] Sponsor's cases were coded as "TSS-like symptoms" and were not further classified based on CDC criteria, so a comparison made on that basis is not possible.

contacted the sponsor. Since it is also expected that the AERS database does not capture all cases, the number of cases of TSS noted in this review, regardless of the data source, in all likelihood reflects an underestimate of the true situation. On that premise and given that TSS is a serious and potentially fatal disease, the persistent reporting of TSS cases is of concern because there should have been a marked decrease in the number of TSS cases reported especially after 1993 when sales dropped down to 5,000.

In order to minimize the risk of TSS with the use of the Sponge, labeling of the Today Sponge should provide clear and easy to understand information to the consumer about the risk of TSS, consequences associated with TSS, as well as information about ways to decrease the small but present risk when using the sponge.

2) Difficult Removal of Sponge

Difficulty removing the Sponge has been reported in the Annual Reports ever since the Sponge was marketed in 1983. Cases reported as difficult removal of sponge from 1990 onwards were reviewed for a general sense of the circumstances surrounding the difficult removal. The information from Medwatch forms indicated that there were cases of difficult removal of sponge that required medical assistance for removal (consumer went to the emergency room or to a physician). In other instances, removal guidance was provided over the telephone. The consumers usually reported back that they were successful, although there were indications from some reports that consumers were instructed to call back with the information. Consumers were also instructed to see a physician if they could not remove the sponge themselves. There were also reports of difficult removal that did not provide any other information about the resolution of the problem.

MO Comments: There should be clear instruction to the consumer about the possibility of retained sponge or sponge parts with difficult removal and they are to seek medical assistance if there is incomplete removal of sponge. Information should be provided that retained sponge/sponge parts for longer than the duration indicated on the label may predispose to vaginal infection, and potentially more serious infection such as TSS. The sponsor should outline a procedure to follow up with consumers who report difficulty with sponge removal and obtain information as to the resolution of the problem.

Implications for Labeling

A. Carton

(1) Clear warning about TSS should be prominently displayed, including information about the signs of TSS, the message that there is a risk of TSS with sponge use, and that death is a possible outcome. The risk of TSS may be avoided by the use of other contraceptives (Some of this information may be placed in the package insert.)

(2) Include general statement about not using the product if there is previous experience of allergy to the active ingredient. This statement should be consistent with all other OTC labeling.

(3) Absolute contraindications to use should include the first 6 weeks after a vaginal delivery, menstrual period, and previous episode of TSS.

(4) Relative contraindication to use should include recent miscarriage or abortion.

(5) Since the sponge is intended for use in the vagina for up to 30 hours, it may be prudent to include that a doctor should be consulted prior to use if there is the

possibility of an existing vaginal infection. For example, proposed class labeling for OTC vaginal antifungal products have the statement: "**Ask a doctor before use if you have** lower abdominal, back or shoulder pain, fever, chills, foul smelling discharge, painful vaginal intercourse (sex), or a missed period. These may be signs of a sexually transmitted disease (STD) or a tubal pregnancy".

(6) The concern remains about alerting the consumer if she develops an infection in the course of sponge use, so the above statement should be repeated "**Stop use and ask a doctor if** you get abdominal pain, fever, chills, or foul smelling vaginal discharge."

B. Package Insert

(1) Warnings

- Toxic Shock Warning as on carton. Inform consumer about the risk of TSS, and that sponge-associated TSS may be avoided by not using the sponge.
- Include all of the warnings under special headers on the carton.
- Provide more information to the warnings on the carton where warranted, e.g.
  - ⇒ explanation of why the sponge should not be used immediately post-partum, or post-abortion/miscarriage: "The Today sponge should not be used any sooner than 6 weeks after a vaginal delivery of your baby. This is to allow enough time for your uterus to return to normal size. If you have had an abortion or miscarriage, your doctor can advise you as to when you can start using the sponge."
  - ⇒ include information about sexually transmitted diseases (STD) including AIDS, and the use of condoms in addition to the sponge for STD protection
  - ⇒ the consumer should know that if they suspect that they may already have an ongoing vaginal infection, they should check with their doctor before using the sponge. Further, if they experience signs of an infection such as abdominal pain, fever, chills, or foul-smelling vaginal discharge while using the sponge, they should remove it immediately and contact their doctor.
  - ⇒ add to the warning about not using the sponge if pregnant. Inform the consumer that a late menstrual period may be an early sign of pregnancy, and if that happens, they should ask a doctor before use.

(2) Directions

- continue with the actual instructions, including point about washing hands, using clean water etc.
  - ⇒ reinforce message about not leaving the sponge in place for more than 30 hours
  - ⇒ reinforce message about not douching with sponge in place
- continue with removal instructions
  - ⇒ reinforce message about difficult removal or incomplete removal, and the referral to the Today's Women Care toll-free line or the physician

(3) Information

- information about the most commonly expected local effects from sponge use should be provided to the consumer
- within the context of current sexual practices, include information about sexually transmitted diseases (STDs), including HIV, increased risks with multiple sexual partners or a new partner, and protection with the use of condoms.

⇒ reinforce message about possibility of a vaginal infection (including STD/HIV) if there are signs of infection, and refer to doctor

Other Recommendations

Information derived from MedWatch reports have been limited. AERS is often used as a signal for further investigation. While not perfect, it is still an organized system serving its purpose of allowing the Agency to keep track of adverse events occurring in association with specific product use. While TSS is a rare event, it is an event with potentially serious consequences, and the re-marketing of the Today Sponge should include consideration of that potential risk. Post-marketing surveillance with careful monitoring of serious adverse events, including TSS should continue. In the occurrence of an event suspicious for TSS, every effort should be made to obtain medical records and all pertinent information for confirmation of TSS.