Field Safety Notice

Product name: PrePex, manufactured by Circ MedTech (CMT)

FSN-identifier: 001_2015

Type of action: advice given by manufacturer regarding use of the device and follow-up with patients.

Date: February 4th, 2015

Attention: Users of the adult male circumcision device PrePex, manufactured by CMT.

Details on affected product:

Three cases of tetanus occurring after PrePex circumcision have been reported in two countries. On Dec 30/11/14, CMT issued a Field Safety Notice (CMT_FSN_001_2014) with the following advice:

> Protective immunity against tetanus toxoid should be confirmed in any individual presenting for placement of PrePex device until completion of the ongoing investigation and further notice;

Since the release of CMT_FSN_001_2014, CMT has conducted and completed its investigation.

Description of the investigation results:

A revision of the risk assessment was conducted for certain aspects of the procedure, including placement and removal. The following gives an update on the risk assessment conducted by CMT.

Risk of infection from the device:

PrePex product samples from the device lots that were used in the 3 procedures where Tetanus occurred were sent to a qualified laboratory for testing of any microorganism. In addition, the company sent 10 randomly selected samples from other lots for testing.

All tested lots came out negative for C. tetani and any other microorganism.

Risk of infection from the necrotic tissue:

In a notice from 8th Dec 2014 the WHO has raised a concern regarding a theoretical risk for C. tetani infection leading to clinical tetanus, due to the biological feature of the necrotic tissue which exists in PrePex but does not exist in surgical circumcision. This theoretical risk led CMT to advice for confirmation of protective immunity against tetanus toxoid until completion of investigation.

CMT commissioned a technical expert who is well published in this field to examine this potential risk. His report (Attached as Appendix 1) contains a thorough analysis of the potential risk to contract clinical tetanus due to the PrePex induced necrotic foreskin.

The CMT expert report has concluded that there is no risk of contracting clinical tetanus due to the necrotic foreskin.

Risk of infection from wound care:

Prior, during and after the PrePex removal inappropriate disinfection of the wound area or lack of such disinfection creates a potential risk for wound contamination.

As with wounds from surgery or trauma in unimmunized persons, the risk of tetanus following circumcision includes potential inappropriate wound care or use of traditional practices of applying substances to the wound such as animal dung or soil which potentially contain C. tetani.

The following actions are recommended on an interim basis to mitigate risk of Tetanus until further notice.

Advise on actions to be taken by the user:

- As for other methods of VMMC, during the PrePex placement and removal, inappropriate disinfection or lack of disinfection has the risk for contamination. Therefore all PrePex users should be re-educated on the disinfection procedure prior to PrePex placement as well as prior and during PrePex removal.
- As for other methods of VMMC, men opting for VMMC by PrePex should receive full information on the benefits and risks of the procedure.
- As for other methods of VMMC, patient information material and counselling should strongly emphasize: to avoid use of potentially C. tetani-containing home remedies over the wound, the risk from these practices and early symptoms of tetanus and the need to seek immediate care for such symptoms.
- The company intends to issue soon an updated Information for Users (IFU) and an additional FSN which will include:
    - Improved disinfection techniques prior to placement as well as prior and during PrePex removal
    - Improved wound care instructions for patients
    - Improved patient counseling
    - Updates regarding the need for C. Tetani immunization prior to PrePex Placement

A meeting of experts will be convened by WHO in early March 2015 to discuss risk management for all types of VMCC. WHO is expected to issue an updated information for users after that time.

Transmission of this Information Notice for Users:

This notice needs to be passed on to all those who need to be aware within your organization or to any organization where PrePex is being used.

Contact person for further information:

Alon Kushnir, e-mail: alon@PrePex.com

Appendix 1

ITZHAK BROOK M.D., M.Sc.
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January 19, 2015

Alon Kushnir
Circ MedTech

Re: Evaluation of the risk of tetanus developing following utilization of PrePex for non-surgical circumcision

Dear Mr. Kushnir,

I have been requested by you to evaluate the risk of tetanus developing following utilization of PrePex for non-surgical circumcision due to the foreskin tissue becoming devitalized and necrotic, and the creation of anaerobic conditions conducive to *Clostridium tetani* growth.

I have reviewed the following materials concerning the above matter.

1. WHO Safety notice (8th Dec 2014)
2. Circ MedTech Field Safety Notice (CMT_FSN_001_2014)
3. Uganda report of 2 cases of Tetanus post PrePex procedure
4. Rwanda report of 1 case of Tetanus post PrePex procedure
5. PrePex Information for Users rev 14
6. PrePex procedure videos – Placements and Removals
7. PrePex photos from day 0 to day 7
8. Photos of PrePex wound on day 7 – good wound and poor wounds
9. Photos of Adverse events including significant Edema following displacement
10. Reports from all PrePex studies

I am an infectious diseases physician with special expertise in anaerobic infections and special interest in clostridial infections. I am herewith attaching a copy of my C.V. After reviewing the above material I am enclosing my opinions regarding the possible risk of developing tetanus associated with performing non-surgical circumcision using PrePex.

Background

Placement of the PrePex band cuts off blood supply to the foreskin and venous and lymphatic drainage from the foreskin, thus inducing its complete atrophy, enabling its non-surgical removal within 7 days. Following the interruption of blood supply and drainage the foreskin develops necrosis that is expected to be associated with polymicrobial aerobic and anaerobic bacteria. Even though *Clostridium tetani* is infrequently isolated from necrotic infections in the perineal area (1), it is possible, that it may also be present in the polymicrobial infection within the foreskin and eventually release its exotoxin (tetanospasmin).

Tetanospasmin enters and travels through the peripheral nerves to the central nervous system, or is carried by lymphocytes. (2) The toxin selectively binds to surface membrane of nerve terminals, followed by uptake and subsequent retrograde axonal transport. (3) Following axonal transport, tetanospasmin eventually effects the peripheral and central nervous system.

Risk of tetanus development after PrePex utilization

Placement of PrePex band causes death of all human cells within the foreskin and the nervous system nerves cells and axons do not survive and function within hours of its application. Clinical studies demonstrated a significant reduction in pain sensation in the foreskin within 8 hours of Prepex placement and a complete skin anesthesia within 16 hours. (4) These sensory alterations are due to anoxic disruption of intracellular neural activity and eventual neural cell death. Active intracellular transportation of tetanoplasmin is not expected to occur in such settings. A complete death of neurons is known to occur within 48 hours of exposure to anoxia in an in-vitro model (5).

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It is unreasonable to assume that *C. tetani* can enter to the foreskin immediately after PrePex application, as the foreskin's surface at that time is intact; providing a barrier to bacterial penetration. In the event *C. tetani* enters the foreskins within the first 48 hours anaerobic conditions necessary for its growth, vegetation and production of tetanospasmin may not exist.

Transportation of tetanospasmin would not be possible following the disruption of the foreskin's neural activity within 8-16 hours of PrePex and the subsequent neural cell and axons death.

The placement of the PrePex band also prevents the transportation of the toxin by lymphocytes or through tissue diffusion into the central nervous system.

Risk of tetanus by the post PrePex removal wound

Following removal of the Prepex band a superficial dry wound around the glans penis is exposed. The wound may become contaminated by environmental or human flora (i.e., skin, gastrointestinal). However, the wound's scar tissue (granulation) that has developed within the past 7 days provides protection from potential deep tissue invasion of potential pathogens including *C. tetani.* Such protection is not provided after surgical circumcision where the wound is deeper and has sutures. These sutures may actually serve as a nidus of infection for potential pathogens including *C. tetani.*

Appropriate wound care is expected to mitigate the potential of wound infection including *C. tetani.*

Conclusions

It is my opinion that the presence of necrotic foreskin during and after a Prepex procedure is not associated with the potential development of tetanus. This is because tetanospasmin cannot enter and/or travel through the devitalized nervous system within the foreskin. Furthermore, no transport of the toxin would be possible by lymphocytes through the PrePex band.

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Sincerely,

Itzhak Brook M.D., M. Sc.

References:

1. Brook I, Frazier EH. Clinical and microbiological features of necrotizing fasciitis. J Clin Microbiol. 1995;33:2382-7
2. Brook I. Current concepts in the management of *Clostridium tetani* infection. Expert Rev. Anti Infect Ther. 2008; 6: 327-336.
3. Schwab ME, Thoenen H. Selective Binding, uptake and retrograde transport of tetanus toxin by nerve terminals in the rat iris. j Cell biol. 1978; 77: 1-13.
4. Mutabazi M, Kaplan SA, Rwamasirabo E, Bitega JP, Ngeruka ML, Savio D, Karema C, Binagwaho A. HIV Prevention: Male Circumcision Comparison Between a Nonsurgical Device to a Surgical Technique in Resource-Limited Settings: A Prospective, Randomized, Nonmasked Trial. J Acquir Immune Defic Syndr. 2012; 61: e49-55.
5. Rosenbaum DM, Kalberg J, Kessler JA: Superoxide Dismutase Ameliorates Neuronal Death From Hypoxia in Culture. Stroke. 1994; 25: 857-862

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