WHO Prequalification of Male Circumcision Devices
PUBLIC REPORT

Product: PrePex
Number: PQMC 0001-001-00

Abstract

PrePex with product codes DW0201, DW0202, DW0203, DW0204 and DW0205, manufactured by Circ MedTech Limited, CE-marked regulatory version, was accepted for the WHO list of prequalified male circumcision devices and was listed on 31 May 2013.

PrePex is a single use, disposable device; indicated for circumcision of adult men, defined as circumferential excision of the foreskin or prepuce at or near the level of coronal sulcus, with minimal amount of preputial skin remaining.

The device should not be used if the package has been compromised. Use by trained personnel only. All device components should not be reused at the risk of cross contamination. The device is intended for adults only and is not applicable for males under the age of 18. The device should be used only in settings where suitable surgical facilities and skills are available within a short time frame (6-12 hours) in order to manage potentially serious complications resulting from device displacements.

Device displacement when wearing the device, may lead to the risk of adverse events. Informing the patient of safe behavior when wearing the device is critical.

PrePex includes the following items:
   1. Placement Ring
   2. Elastic Ring
   3. Inner Ring
   4. Verification Thread

Accessories:
The PrePex Sizing Plate (PSP) is intended for single use for selecting an appropriate device size.

The use of PrePex requires additional tools and materials which are not supplied with PrePex.

For Placement: examination gloves, antiseptic solution, skin marker, gauze, 5% anesthetic cream and nurse utility scissors.
For Removal: examination gloves, antiseptic solution, sterile harvey wire scissors, sterile forceps, sterile spatula, sterile scalpel, 2 wound dressings, nurse utility scissors and a cutter.

Storage:
The test kit should be stored at -10 to 55 °C.

Shelf-life:
3 years.

**Summary of prequalification status for PrePex**

<table>
<thead>
<tr>
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<th>Initial acceptance</th>
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<tbody>
<tr>
<td><strong>Status on PQ list</strong></td>
<td>31 May 2013</td>
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<tr>
<td><strong>Dossier assessment</strong></td>
<td>08 October 2012</td>
</tr>
<tr>
<td><strong>Inspection status</strong></td>
<td>30 January 2013</td>
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<tr>
<td><strong>Clinical study</strong></td>
<td>28 February 2013</td>
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MR: Meets Requirements
NA: Not Applicable

Prepex was accepted for the WHO list of prequalified male circumcision devices on the basis of data submitted and publicly available information.

**Background information**

Circ MedTech Limited submitted an application for prequalification of PrePex. Based on the established prioritization criteria, PrePex was given priority for prequalification.

**Product dossier assessment**

Circ MedTech Limited submitted a product dossier for PrePex as per the Instructions for compilation of a product dossier (PQMC_018 v1). The information submitted in the product dossier was reviewed by WHO staff and external experts (assessors) appointed by WHO in accordance with the internal report on the screening and assessment of a product dossier (PQMC_009 v1). Based on the product dossier screening and assessment findings, a recommendation was made to accept the product dossier for PrePex for prequalification.

Commitments for prequalification:
The manufacturer has amended and submitted additional documentation as per the product dossier assessment findings. No further amendments are required.
Manufacturing site inspection

A comprehensive inspection was performed at the site of manufacture Circ MedTech, 6 Hahoshlim St., 1st Floor Herzelia, 46722, Israel and 3BY, 24959 Industrial Park, P.O. Box 65, Migdal Tefen, Israel of the PrePex test in 18-19 January 2012 and a re-inspection of the same two sites was performed in 5-7 November 2012 as per the Information for manufacturers on prequalification inspection procedures for the sites of manufacture of diagnostics (PQDx_014 v1). The inspection found that the manufacturer had an acceptable quality management system and good manufacturing practices in place that ensured the consistent manufacture of a product of good quality. The manufacturer's responses to the nonconformities found at the time of the inspection were accepted 30 January 2013.

Commitments for prequalification:
1. The manufacturer has committed to continuing improvements in the quality management system particularly in the areas of documented procedures to ensure that supplied product conformed to specified purchase requirements, planned controlled conditions to ensure consistent quality of manufactured product particularly at scale up and internal audits to assure the QMS conformed to planned arrangements.
2. The manufacturer has committed to effective communication of accurate information to customers/end users, planned arrangements for verifying that product requirements have been met, compliance with management review requirements and defined operations for labeling and packaging together with ongoing communication over time to finalize any outstanding issues noted in the WHO responses to the inspection findings.

Clinical study

The WHO Technical Advisory Group (TAG) on Innovations in Male Circumcision concluded that the range and scope of clinical studies met the WHO requirements for evaluation of a device; and demonstrated that, for the purposes of HIV prevention, the PrePex device can efficaciously and safely circumcise healthy males over 18 years, when used by suitably trained providers, and when surgical backup facilities and skills are available to manage device displacements or early removals that could result in serious complications. The TAG advised that: effective training materials are available and PrePex providers are appropriately trained; men receive accurate information on safe device use and risks while wearing a device, and PrePex is used only in settings where suitable surgical facilities and skills are available within a short time frame (6-12 hours). This conclusion is time-limited and must be reassessed in about one year when more experience and data are generated to further inform safe use.

Studies reviewed: eight studies from 3 African countries satisfactorily met the criteria in the WHO Framework for Clinical Evaluation of Devices. All studies included only healthy males 18 years and older. The device was placed successfully on 2417 eligible men.
Device use
Eligible: males 18 years and older; without contraindications to conventional male circumcision surgery, and additionally, without contraindications specific to PrePex device: including phimosis, narrow foreskin, tight frenulum, adhesions.
Among males on whom the device was placed, 99.5% had a successful circumcision without surgical intervention and a resulting wound line without suture marks.

Requirements for device use: At least two visits are required; during the interval the client must wear the device
- Placement: adequate supply of all device sizes plus accessory supplies and two trained providers, clean procedure, local topical (not injectable) anesthesia.
- While wearing the device for 1 week: analgesia as needed, and access within six to twelve hours to conventional surgical skills and facilities to manage device displacements or early removals (including self-removals) and prevent serious long-term sequelae.
- Removal: requires a clean setting and some sterile accessory equipment. Accessory supplies and equipment are not provided by the device manufacturer.

Safety, healing and discomforts:
All AEs observed in studies were reviewed and classified by the TAG in a uniform manner, guided by internationally recognized principles and definitions of AEs and serious adverse events (SAEs) (Global Harmonization Task Force) which differed somewhat from the definitions and classification used by study investigators.

Adverse events occurred among 1.7% of participants; the majority were Mild and Moderate, while 0.4% were considered Serious as prompt surgical intervention was required to prevent serious long-term sequelae (in all cases surgical intervention was successful with no complications and satisfactory outcomes). The AE rate was lower among men who had PrePex circumcision than among men who had conventional surgery, but this difference was not statistically significant. No mechanical failures were reported. Healing time appears to be about 1 – 2 weeks longer than following conventional surgical circumcision. Some pain occurs with PrePex procedures, primarily during the first few days after placement and briefly on removal of the device. Complaints of unpleasant odour were also noted by some study participants and providers.

Client information must clearly indicate that once placed, the device must remain for seven days; in case a client desires to remove the device, clients must be instructed to return to the clinic and conventional surgery will be required to complete the circumcision. Clients must also be instructed on safe behaviours while the device is worn, including avoidance of sexual activity and masturbation, the risks associated with misuse and possible surgical intervention required. Clients need to be informed of the possibility of displacement, pain and/or odor while wearing the device.
Labelling

1. Labels
2. Instructions for use
1. Labels
2. Instructions for use
User Manual for Authorized & Trained Users Only

Intended use:
PrePex is a single use, disposable device; indicated for circumcision of adult men, defined as circumferential excision of the foreskin or prepuce at or near the level of the coronal sulcus, with minimal amount of preputial skin remaining.

Contraindications:
Dermatitis of the penis or foreskin, allergy to rubber, non-intact skin on the penis or foreskin, active genital infection, warts on the glans or the inner surface of the foreskin, anatomic abnormality including phimosis, paraphimosis, torn or tight frenulum, hypospadias, epispadias, any active penile diseases, active infectious disease impairing health, history of bleeding disorders, narrow foreskin opening.

Disposal:
Follow local, state and federal regulations with respect to environmental protection when disposing of general and infectious waste. If there are no regulations, the infectious waste, including all device elements, tools and materials that came in contact with the body or with body fluids should be incinerated. Other general waste should be segregated and stored in bins marked “General”. The waste should then be buried in a designated area.

Caution:
The device should not be used if the package has been compromised. Use by trained personnel only. All device components should not be reused at the risk of cross contamination. The device is intended for adults only and is not applicable for males under the age of 18. The device should be used only in settings where suitable surgical facilities and skills are available within a short time frame (0-12 hours) in order to manage potentially serious complications resulting from device displacements.

Device displacement when wearing the device, may lead to the risk of adverse events informing the patient of safe behavior when wearing the device is critical.

Clinical Experience:
Three clinical studies of PrePex were performed in Rwanda according to the WHO official Evaluation Framework of Adult Male Circumcision (MC) Devices.

1. A study that demonstrated the safety & efficacy of the PrePex device in 105 male subjects. Results: All subjects achieved circumcision with 1 case of diffuse oedema after device removal, which resolved with minimal intervention. Pain was minimal with brief discomfort during device removal. The entire procedure was bloodless, requiring no anaesthesia, no suturing, and no sterile settings. Subjects had no sick/absent days associated with the procedure. Median time for complete healing was 21 days after device removal. There were no instances of erroneous placement and no mechanical problems with the device. Conclusion: The PrePex device was found to be safe and effective.

2. Randomized controlled study, comparing the safety and efficacy of the PrePex in 144 adult male subjects to a surgical circumcision method in 73 adult male subjects. Results: All subjects were circumcised in 10 working days. The nonsurgical MC mean procedure time of 3.1 minutes (skin to skin), was significantly shorter than the mean surgical procedure time (15.4 minutes skin to skin) (P = 0.0001). There were no device-related adverse events. Healing time of the PrePex arm was longer than the surgical arm. Conclusion: PrePex nonsurgical MC, takes significantly less time than surgical, is as safe, does not require injections or sterile settings, is bloodless and seems to be suitable for nurses.

3. A Cohort field study that demonstrated the safety and efficacy of the PrePex on 518 adult males, when the procedure is performed by nurses. Results: All 518 subjects from the pilot and pivotal phases achieved complete circumcision. There were 5 AEs on 4 subjects (rate of 0.96%, 95% Confidence Interval: 0.31-
2.24. AEs were moderate and were resolved with simple intervention.
Conclusions: The study demonstrated that nurses can be easily trained to
perform safe and effective circumcisions using the PrePex device.

Environmental Requirements and Storage Conditions:
Storage: -10°C to 55°C, away from direct sunlight, humidity up to 80%.

Shelf Life:
The PrePex has a shelf life of 3 years.

Device Overview:
PrePex includes the following items:
1. Placement Ring
2. Elastic Ring
3. Inner Ring
4. Verification Thread

![PrePex components](image)

Accessories:
The PrePex Sizing Plate (PSP) is intended for single use for selecting an appropriate
device size.

![The PrePex Sizing Plate (PSP)](image)

The use of PrePex requires additional tools and materials which are not supplied with
PrePex. For Placement: Examination Gloves, Antiseptic solution, Skin Marker,
Gauze, 5% Anesthetic Cream and Nurse Utility Scissors. For Removal: Examination
Gloves, Antiseptic solution, Sterile Harvey Wire Scissors, Sterile Forceps, Sterile
Spatula, Sterile Scalpel, 2 Wound dressings, Nurse Utility Scissors and a Cutter.

Patient Screening:
Before performing the procedure, screen the patient for any contra indication, and
physically test if the opening of the foreskin is wide enough for the PrePex procedure.
Perform the test with examination gloves. Stretch the foreskin as described in step 6
of the Placement procedure below, and visually assess the flexibility of the foreskin
and the opening. If there is pruritus or tight frenulum (i.e. the opening is not wide
enough for the inner Ring insertion), the patient should be contra indicated for
PrePex. Gently pull down the foreskin to expose the sulcus and examine whether the
foreskin is tight in the area below the sulcus. If the foreskin is tight in the area below
the sulcus, the patient should be contra indicated for PrePex.
Patient Preparation:
During the Prepex MC procedure, providers should wear examination gloves.

Prepare the skin with an antiseptic solution, starting with the glans and the shaft of the penis, and moving out to the periphery, as per the WHO Manual for Male Circumcision Under Local Anesthesia. ¹

1. Use a new, single-use Prepex Sizing Plate (PSP). Select the appropriate size A, B, C, D, or E by sliding each opening of the PSP over the glans and placing it directly under the corona sulcus. The appropriate size is the opening which fits best. (figure 3)

2. Choose Prepex based on the sizing outcome (A, B, C, D or E).

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<th>Type</th>
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<tr>
<td>B</td>
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Note – If the diameter under the corona sulcus is too large and it cannot fit in to the E opening or if it is too small and it cannot fit precisely to size A, do not perform the Prepex procedure and refer the patient to surgical circumcision.

Procedure preparation:

1. Mark the outer circumcision line according to the WHO Manual for Male Circumcision Under Local Anesthesia (Chapter 5-15, and Fig 5.17, Chapter 5-27 and Fig 5.33 and Fig 5.34) using a standard medical skin marker only (figure 4).

2. This step is common to all of the methods of circumcision. Stretch the foreskin past the glans and release. When the foreskin has returned to a natural “resting” position, indicate the intended line of the circumcision with a skin marker. The line should correspond with the corona, just under the head of the penis. Some uncircumcised men have a very lax foreskin, which is partially retracted in the resting position. In such cases it is better to apply a little tension to the foreskin before marking the circumcision line. However, it is important not to pull the foreskin too hard before marking the line, as this will result in too much skin being removed.

3. Mark the intended circumcision line, as described above, with a V shape, pointed towards the frenulum, on the underside (ventral aspect) of the penis (figure 5). The apex of the V should correspond with the midline raphe. Make sure the V shape is not too sharp.

Make sure that the marked circumcision line will not be erased during the Prepex procedure. If the marking is not clearly visible do not perform the procedure. Before continuing it is very important to mark the line again, if necessary.

4. After verifying that the line marking is clear, pull the foreskin down towards the body and apply 1gr of 5% anesthetic cream on the exposed shaft area up to the coronal sulcus. Once the anesthetic cream has been applied, there is no need to wait for the anesthetic cement to take effect and the procedure can commence immediately.

Placement Procedure:
1. Place the Elastic Ring on the Placement Ring (see figure 6). Do not remove the Verification Thread; it is intended to correct Elastic Ring misplacement.

2. Place the Placement Ring (with Elastic Ring in place) on the penis shaft with the Elastic Ring side facing away from the body (See figure 7).

Steps 3 and 4 should be performed by 2 people.

3. The first person should stretch the foreskin up and to the sides for insertion of Inner Ring, holding the foreskin dorsal and ventral sides. Use fingers or a dry gauze for a good grip (See figure 8). Ensure that the foreskin is fully stretched by viewing the sulcus area, thus assuring there will be no double entrapped foreskin.

4. The second person should insert the Inner Ring with its flat parts toward the dorsal and ventral penis sides into the opening of the foreskin (see figure 9), assuring that one of the flat sides is in the area of the frenulum and the other flat side is on the opposite side of the frenulum.

5. Warning: When introducing the Inner Ring through the foreskin opening, be very careful not to harm the foreskin. If it is impossible to introduce the Inner Ring do not perform the procedure.

6. Introduce the Inner Ring over the glans and place it just below the glans (on the sulcus).

7. Hold the foreskin closed at the tip of the penis to secure the Inner Ring in place (See figure 10). Advance the Placement Ring and Elastic Ring towards the glans until you can visually see that the Elastic Ring is circumferentially just over and inside the Inner Ring groove and that the Elastic Ring and Inner Ring are aligned.

8. Once the Elastic Ring and Inner Ring are aligned, with one hand support the Placement Ring, with the other hand adjust the foreskin so the marked circumcision line is exactly underneath the Elastic Ring. Adjust the foreskin from beneath each of the 4 Legs by pulling the skin downwards (See figure 11).

9. To place the Elastic Ring - Using 4 fingers of your dominant hand hold the Elastic Ring and Inner Ring together in the space between each of the 4 Placement Ring Legs. Work with the thumb and finger of your non dominant hand to release the Elastic Ring from one Placement Ring Leg at a time (figure 12).

10. Make sure the Elastic Ring is mounted directly over the Inner Ring groove and above the marked circumcision line previously marked. If the Elastic Ring is not positioned as desired or if you identify that there is double entrapped foreskin, use the
verification thread to pull it off the penis and start the procedure again.

11. Upon proper placement of the Elastic Ring, discard the Placement Ring, and cut the verification thread with the nurse utility scissors.

12. Supply the patient with 2 tablets of 400Mg ibuprofen or other painkillers tablets and Post Placement information.

**Instruct the patient on the following before sending him home:**

a. Not to move the Device, not even through clothes – emphasize that touching the device while urinating or bathing must not cause any movement of the device. Any movement of the device may lead to surgical MC.

b. To return for device removal after 7 days. Early removal may result in surgical MC.

c. To return to the MC center if he wants to remove the device before the 7 days period is over.

d. Not to remove the device and not to let anyone other than the designated provider to remove the device.

e. To report any unexpected situation, such as uncontrollable pain or device displacement.

f. Not to pull on the foreskin in case partial detachment

g. To abstain from sexual intercourse and to avoid masturbation when the device is on the penis, so it will not move out of place.

**Inform the patient of the following when sending him home:**

a. He may experience pain in the following weeks, and he should take the supplied painkiller tablets to control the pain.

b. The foreskin distal to the Elastic Ring will become darker and dry.

c. Unpleasant odor may occur while wearing the device.

d. Infection may occur while wearing the device.

e. There may be some partial skin detachments along the Elastic Ring.

f. He should bath normally and keep the inner foreskin clean. The area should be rinsed thoroughly (holding the source of water close to the penis and directing the water stream to the foreskin opening) without touching and/or displacing the device in any way.

**Foreskin Removal:**

1. The device is removed 7 days after it has been placed.

2. It is recommended to use sterile Harvey wire cutting scissors (figure 13), due to their blunt edges and serrated blades, specifically designed to cut tough tissue like the dried necrotic foreskin.

3. Before removing the foreskin it is recommended to pull the penis and foreskin gently upwards to separate the foreskin from the glans. You may drip fluids (e.g. Antiseptic solution) through the foreskin opening to enhance this separation.

4. Warning: Take care not to injure the urethra through introduction of wire cutting scissors into the meatus or lacerate the glans by not holding the foreskin far enough away from it when cutting.

5. If the opening of the foreskin is very narrow, you should dilate it gently with the forceps tip to allow insertion of one of the wire cutting scissors blade. Use sterile forceps to hold the foreskin and to pull it away from the glans.

6. The foreskin should be cut first vertically toward the Elastic Ring and then with an angie, spirally, to the line that the Inner Ring is visible (figure 14).

7. Cut the foreskin as close to the Elastic Ring as possible, so that the tip of the Inner Ring becomes visible.
Elastic Ring Removal:
1. Warning: Elastic Ring should be removed only after the foreskin has been removed.
2. Use a sterile scalpel to cut the Elastic Ring placed over the flat part of Inner Ring on the side that is opposite the frenulum. Do not cut the Elastic Ring on the same side as the frenulum (Figure 15).
3. Take care not to harm the viable skin.

Inner Ring Removal:
1. The Inner Ring is removed after the Elastic Ring removal.
2. Use a sterile spatula to separate the necrotic foreskin all around the Inner Ring.
3. Pull the inner ring out on a curved side using the spatula; take care to avoid the frenulum (Figure 16).
4. Partial separation of the necrotic foreskin may occur, in such cases extra care should be taken when extracting the Inner Ring to minimize pain at the separation area.
5. Cut the Inner Ring with a cutter before discarding it.

Post Removal Procedure:
1. Clean the circumcised penis with antiseptic solution.
2. Dress the circumcised penis with a standard non-adherent pad.
3. Instruct the patient not to wet the dressing for 2 days.
4. Supply the patient with a new dressing to take home and instruct him that in case the dressing on the penis gets wet he should remove it and replace it with a new dry dressing.
5. Instruct the patient to remove the dressing completely in 2 days, at which time he can wash the penis and the wound area normally.
6. Instruct the patient to contact the MC clinic in case of pain, infection, swelling or fever. Inform the patient that all of those risks may occur following device removal.
7. Instruct the patient to abstain from sexual intercourse for 6 weeks after device removal and to avoid masturbation, and that those actions may lead to disruption of the wound which will result in delayed healing.
8. Explain to the patient the importance of using condoms, and that circumcision is not a complete protective solution for the prevention of HIV infection.

Procedure and Device Associated Risks:
The following possible risks may occur while the patient is wearing the PrePox:
- Patient displacing the device from its original position may lead to pain and to diffuse oedema that will require surgical MC.

To mitigate such risks it is essential to explain to the patient that he should not move the device even if he has pain or discomfort, and he should not masturbate or have sex. In case of pain the patient should take the supplied painkiller tablets. If the pain is uncontrollable, the patient should return to the MC center to be evaluated and clinically managed. Early controlled removal of foreskin and device may be indicated. If there is displacement of the device with or without oedema, the patient should return to the clinic as soon as possible where the provider may recommend surgical circumcision to avoid serious and possible life threatening infection. Surgical circumcision should be performed within 6-12 hours after displacement.

The following possible risks may occur as a result of misusing the device by provider:
- If the Inner Ring is not pushed all the way down to the sulcus level this may lead to disturbance of urine flow.
- If the Inner Ring is not pushed all the way down to the sulcus level this may lead to insufficient removal of foreskin.
- If the circumcision line is not marked according to recommendations presented in this document, this may lead to removal of too much foreskin and future problems with penile function, or to removal of insufficient skin.
- Penile injury during foreskin removal due to misuse of the wire cutting scissors.

Other possible risks:
- Device displacement and oedema requiring urgent surgical circumcision.
- Bleeding after device removal.
- Pain – mainly 2 days after Placement procedure.
- Infection while wearing the device and after removal.
- Delayed healing.
- Injury to the penis particularly during removal.
- Unpleasant odor while wearing the device.

It is important to report any complaint or incident occurring with the device to the manufacturer Circ MedTech, by Email or phone as soon as possible.

Training:
To receive complete training materials, including presentations and videos, send an E-mail to info@borepex.com requesting the training material and a CD will be sent as soon as possible.
References:

<table>
<thead>
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<th>Must Consult Instructions for use</th>
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<td>Product meets the requirements of the applicable European Directive.</td>
<td>Do not reuse</td>
<td>MedNet GmbH * Borkstrasse 10, 48163 Muenster, Germany Phone +49 251 32266-0</td>
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www.Prepex.com

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