CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:

Chlorhexidine-impregnated sponge dressing for prevention of catheter exit site infection in incident peritoneal dialysis patients – a pilot study

PROTOCOL VERSION: 2.0
PROTOCOL DATE: 04 Oct 2017

PRINCIPAL INVESTIGATOR:

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PROTOCOL SIGNATURE PAGE

Protocol Title: **Chlorhexidine-impregnated sponge dressing for prevention of catheter exit site infection in incident peritoneal dialysis patients – a pilot study**

Protocol Version: Version 2.0

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Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and Singapore Guideline for Good Clinical Practice (SGGCP).

Principal Investigator Name: _____Htay Htay_____

Principal Investigator Signature: _____Htay_____

Date: _____04.10.2017_____

1 BACKGROUND AND RATIONALE

Peritoneal dialysis-related infection is one of the commonest reasons for patients to discontinue peritoneal dialysis (PD) therapy(1). Prevention of infection is of paramount importance for a successful PD programme. The catheter ESI can lead to tunnel tract infection and subsequently peritonitis, which is one of serious complications in PD(2,3). The International Society for Peritoneal Dialysis (ISPD) guidelines recommends regular application of topical antimicrobial agents, including mupirocin or gentamicin at the catheter exit-site to prevent ESI(4). However, the use of mupirocin has been reported to be associated with increased incidence of drug resistant micro-organisms(5–7). The mupirocin was used as the topical antimicrobial agents for exit-site care for PD patients in Singapore General Hospital before the period of 2013. However, the use of mupirocin was withdrawn from the hospital due to increasing evidence of methicillin-resistent *Staphylococcus aureus* (MRSA) which was attributed to the increased use of mupirocin cream(7). Similarly, the use of gentamicin was reported to have a trend towards increased incidence of fungal exit site infection (8). Hence, the alternative antimicrobial agent is warranted to prevent the ESI in PD patients

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1.1 General Introduction

Chlorhexidine is an antimicrobial agent which is effective against both Gram-positive and Gram-negative micro-organisms(1,2). The use of chlorhexidine-impregnated dressing at central venous catheter exit site has been reported to significantly reduce the catheter-related infection in a meta-analysis(3). Moreover, the chlorhexidine-impregnated sponge dressing is required to change once a week only. There is no previous study on the role of chlorhexidine-impregnated sponge dressing in the prevention of exit-site infection in PD patients.

References

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1.2 Rationale and Justification for the Study

1.2.1 Rationale for the Study Purpose

Catheter-related infection is one of the common reasons for peritoneal dialysis patients to discontinue PD therapy. The use of topical antibiotics cream at the catheter exit-site is recommended by International Society for Peritoneal Dialysis to prevent exit-site infection. However, the daily use of antibiotics cream at exit-site is reported to be associated with emergence of drug resistance organisms. Hence, the alternative antimicrobial agent (antiseptic) is needed to prevent exit-site infection in PD patients. In addition, the requirement of daily use of the cream by patients may potentially results in poor adherence to antibiotics application. Chlorhexidine is antiseptic agent and is active against both Gram-positive and Gram-negative organisms. The chlorhexidine-impregnated sponge dressing is required to change once a week only. There is no previous study on the role of chlorhexidine-impregnated sponge dressing in the prevention of exit-site infection in PD patients.

1.2.2 Rationale for Doses Selected

In the present study, the chlorheidine impregnated sponge will be changed once every 7 days as previous randomized study showed non-inferiority of 7 days versus 3 days dressing change in prevention of catheter-related blood stream infection in critically ill adult patients (1)

1. Timsit, J.-F. *et al.* Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA* **301,** 1231–1241 (2009).

1.2.3 Rationale for Study Population

Incident peritoneal dialysis (PD) patients will be recruited in the study. This is to prevent the cross over effect of topical antibiotics in the prevalent PD patients.

1.2.4 Rationale for Study Design

The prospective cohort study is proposed as it is a pilot study only.

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

We hypothesize that the use of weekly chlorhexidine-impregnated sponge dressing at the catheter exit site is safe and effective in the prevention of exit site infection in incident peritoneal dialysis patients

2.2 Primary Objectives

The primary aim of study is to examine the exit-infection rate in patients using chlorhexidine-impregnated sponge dressing.

2.3 Secondary Objectives

The secondary aim of the study is to examine the time to the first episode of exit-site infection, peritonitis rate, time to first episode of peritonitis, infection-related hospitalization, technique failure rate, mortality and adverse events and patient satisfaction with the use of chlorhexidine-impregnated sponge dressing

2.4 Potential Risks and Benefits:

2.4.1 Potential Risks

The common reported risk with use of chlorhexidine-impregnated sponge dressing is local skin irritation or contact dermatitis. The rare adverse event includes severe contact dermatitis which required removing the dialysis catheter, generalised allergic reactions and anaphylactic shock.

2.4.2 Potential Benefits

Chlorhexidine-impregnated sponge dressing can potentially be benefit for patients who are at high risk for exit site infection due to inability to clean the exit site daily including elderly, obese patients, patients with poor visual acuity etc. The use of weekly chlorhexidine-impregnated sponge dressing will also free patient from daily cleaning of exit site, which might provide extra-time for patients to enjoy other activities and potentially may improve the quality of life.

With the data collected from this pilot study, an adequately powered randomised controlled trial could be conducted to compare the effectiveness of once a week chlorhexidine-impregnated sponge dressing with daily topical anti-microbial cream in preventing exit site infection. If successful, our study has the potential to change current clinical practice and improve patient's outcomes.

3 STUDY POPULATION

3.1 List The Number and Nature of Subjects to be Enrolled.

Total of fifty incident peritoneal dialysis patients follow-up at Singapore General Hospital will be recruited for study.

3.2 Criteria for Recruitment and Recruitment Process

Potential participants will be referred by their treating physicians during admission to hospital for initiation of peritoneal dialysis or from clinic. The eligible patients will be approached by one of investigators for recruitment and informed consent will be taken from the patients.

3.3 Inclusion Criteria

All adult incident peritoneal dialysis patients between 21 to 90 years old, who are followed up in Singapore General Hospital

3.4 Exclusion Criteria

Patients with the following conditions will be excluded from the study

1. patients who have known history of allergy to chlorhexidine
2. patients who had previous history of peritoneal dialysis catheter exit-site infection
3. patients with mentally challenging conditions who are unable to give the valid consent for the study
4. patients who have been involved in the another study for exit site infection

3.5 Subject Replacement

There will be no replacement for participants who dropout from study for various reasons.

4 STUDY DESIGN

This a single centre, prospective cohort study.

4.1 Randomisation and Blinding

Not applicable

4.2 Contraception and Pregnancy Testing

Not applicable

4.3 Study Visits and Procedures

The participant will be followed up at 2, 6, 12, 24, 36 and 52 weeks of study and during each visit, the catheter exit-site will be examined by one of the investigators for any sign of infection or allergic reaction, and questionnaires about satisfaction with use of study material (biopatch) will be asked by a study team member at the 12 week of study. Each participant will be followed up for one year. After one-year of study period, there will not be additional follow-up for study purpose, however, participants will be continued followed up in SGH as per routine PD patients' schedule.

4.3.1 Screening Visits and Procedures

Potential participants will be referred by their treating physicians during admission to hospital for initiation of peritoneal dialysis or from clinic. Potential participants will be screened by one of investigators for recruitment and informed consent will be taken from the patients if eligible. No additional visit or additional blood test is needed for screening the participants.

4.3.2 Study Visits and Procedures

If potential participant is agreeable to participate in the study, the informed consent will be taken and participant will be taught how to use the chlorhexidine-impregnated sponge dressing by investigator. The chlorhexidine-impregnated sponge will be applied at the catheter exit-site. Participants will be observed for half an hour for anaphylactic reaction in the peritoneal dialysis centre after the application of chlorhexidine-impregnated dressing for the first time. Participants will be instructed to report any allergic reaction or discomfort or itchiness at the catheter exit-site. Participants will be instructed to change the sponge dressing at once a week, unless the dressing is soiled. Participant will be required to visit clinic at per schedule described above, and to be assessed by the investigator for any adverse effect and any sign of infection at catheter exit at each clinic visit.

4.3.3 Final Study Visit:

The final visit will be 52 week of study. There will be no additional procedure or instruction to participants with regards to the study during the final visit. However, participants will be taught

how to use the standard exit-site care as per centre protocol.

4.3.4 Post Study Follow up and Procedures

There will be no additional follow up for participants for study purpose. However, participants will be followed up as per routine clinic schedule for PD patients as per centre protocol.

4.4 Discontinuation/Withdrawal

4.4.1 Discontinuation Criteria

The participant will be discontinued from the study if he or she develops adverse effects related to the use of chlorhexidine-impregnated sponge dressing, which includes local cutaneous skin reaction at exit-site, contact dermatitis at exit-site or developed exit-site infection.

4.4.2 Discontinuation Visit and Procedures

If participant is withdrawn from the study due to adverse effects, he/she will be treated as per routine recommended practice for the adverse event and will be scheduled to follow up in clinic. The frequency and interval of follow up will be depended on the clinical condition.
If participant voluntarily withdrawal from the study, he/she will be followed up as per routine clinic schedule, which is once every 3 months.

5 TRIAL MATERIALS

The chlorhexidine impregnated sponge, named biopatch, is a protective disk (2.5 cm x 0.7 cm), which is hydrophilic polyurethane absorptive foam with chlorhexidine gluconate, in average of 86.8mg per disk.

5.1 Trial Product (s)

Refer to package insert in Appendix 2.

5.2 Storage and Drug Accountability

The product (biopatch) should be stored between 15C and 30C (59F and 86F), in the original packing. The expiratory date of product is indicated as year (4 digits) and month (2 digits). The product expires after the last day of the month indicated. The study material (biopatch) will be kept in the store room with temperature of 23 to 25 C, in peritoneal dialysis centre.

6 TREATMENT

6.1 Rationale for Selection of Dose

The biopatch disk (chlorhexidine impregnated sponge) comes with 3 sizes, (2.5 x 0.4cm; 92mg) (2.5 x 0.7cm; 52.5mg) (1.9 x 1.5 cm; 86.8mg). The outer diameter of the peritoneal dialysis catheter is 0.5cm, hence, the disk with larger diameter (2.5 x 0.7 cm with 86.8mg of chlorhexidine gluconate) will be used in the study.

6.2 Study Drug Formulations

The study material, which is chlorhexidine-impregnated sponge, comes with sterile package. Each package contains a single disk. The participants will be provided with sufficient number of packages to be used till the next clinic appointment.

6.3 Study Drug Administration

The skin around the catheter exit-site will be cleaned with 10% provodine iodine swabstick as per centre protocol, followed by drying the skin with sterile gauze. Then place the chlorhexidine-impregnated sponge (biopatch) around the catheter with blue printed side is facing upward and the white foam side, which releases the chlorhexidine gluconate, should be in contact with the skin.

6.4 Specific Restrictions / Requirements

Not applicable

6.5 Blinding

Not applicable

6.6 Concomitant therapy

Any topical cream used at the catheter exit-site will be documented.

7 SAFETY MEASUREMENTS

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect
- is a medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.2 Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to CIRB

Reporting of adverse events involves the PI submitting to the approving CIRB the completed SAE Reporting Form within the stipulated timeframe. PI is responsible for informing the institution representative (local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- SAE that result in death, regardless of causality, should be reported immediately - within 24 hours of the PI becoming aware of the event.
- Local life-threatening (unexpected/ expected) SAE should be reported no later than 7 calendar days after the Investigator is aware of the event, followed by a complete report within 8 additional calendar days.
- Local unexpected SAE that are related events, but not life-threatening, should be reported no later than 15 calendar days after the investigator is aware of the event.
- An increase in the rate of occurrence of local expected SAE, which is judged to be clinically important, should be reported within 15 calendar days after the PI is aware of the event.
- Local expected SAE should be reported annually (together with Study Status Report for annual review).
- Local unexpected and unlikely related SAE that are not life-threatening should also be reported annually (together with Study Status Report for annual review).
- Local unexpected AE that are related events should be reported at least annually (together with Study Status Report for annual review).
- Non-local unexpected SAE that are fatal or life threatening and definitely/probably/possibly related should be reported not later than 30 calendar days after the PI is aware of the event.

7.3 Safety Monitoring Plan

Patient's wellbeing and safety will be taken into considerations continuously during the trial period. If there is any contraindication observed during the interim of the study procedure that requires the discontinuation of the procedure, decision shall be made by the PI and Co-Investigators to discontinue the patient from the study.

7.4 Complaint Handling

Complaints will be handled by individual investigators who have direct contact with the patient and/ or have recruited the patient for the study.

Effort will be made by the PI or co-investigators in the study team to explain carefully the study procedure and visits to avoid any confusion.

8 DATA ANALYSIS

8.1 Data Quality Assurance

All measurements will be performed by experienced operators and the data quality will be assessed at the time of acquisition.

8.2 Data Entry and Storage

Electronic data will be stored in a secure database in the Department of Renal Medicine. The use of the data from the study will be controlled by the principal investigator.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

This is just a pilot study only and hence there is no calculation of sample size and power.

9.2 Statistical and Analytical Plans

a. General Considerations

The primary outcome, which is exit-site infection rate, will be analysed using the Poisson regression and the secondary outcomes, time to first episodes of exit site infection, time to the episode peritonitis will be analysed by Cox regression and Kaplan Meier survival curve with log rank

b. Safety Analyses

The exit-site infection rate of the study cohort will be compared with the exit-site infection of historical cohort to examine any significant difference between two cohort in term of infection and adverse effects.

c. Interim Analyses

No interim analyses will be performed for this pilot study.

d. Describe the types of statistical interim analyses, including their timing.

NA

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The data will be collected by research coordinators/investigators using the excel sheet at a regular interval of once a month. Principal investigator will be responsible for evaluation of data quality and data evaluation will be done once every 3 month.

12 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Singapore Good Clinical Practice and the applicable regulatory requirements.

This final study protocol, including the final version of the Patient Information and Informed Consent Form, must be approved in writing by the Centralised Institutional Review Board

(CIRB), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

12.1 Informed Consent

Consent will be taken by PI or other study team members involved in consent taking, such as other delegated renal doctors in the study after patient eligibility has been confirmed. An English informed consent form (ICF) will be used for consent taking. For non-English speakers, a translator will translate the ICF and an impartial witness will witness the consent taking process. For illiterate or non-writing individual, they can use thumbprints instead of signatures and an impartial witness will be present when consent is taken.

12.2 Confidentiality of Data and Patient Records

The information or data related to participants will be kept strictly confidential. The participants will be de-identified in the data collection form.
Electronic data will be stored in a secure database in Singapore General Hospital. The use of the data from the study will be controlled by the PI.

13 PUBLICATIONS

The outcome of this study will be presented at national and international meetings and published in peer-reviewed journals. We would consider authorship to include all of the following: 1) conception and design or analysis and interpretation of data, or both; 2) drafting of the manuscript or revising it critically for important intellectual content; and 3) final approval of the manuscript submitted. Participation solely in the collection of data does not justify authorship but may be appropriately acknowledged in the Acknowledgment section.

14 RETENTION OF TRIAL DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation will be retained by the PI in a secure cupboard with locker. The records will be made accessible for inspection and copying by authorized authorities. We will retain the records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation should be retained by the PI in a secure storage facility for at least 15 years after the study closes.

All electronic data is stored securely in our in-house database. All hard copies of data will be stored under lock and key in the respective PI and Co-I's hospital.

15 FUNDING and INSURANCE

The study is funded by Singhealth NIG grants.

List of Attachments

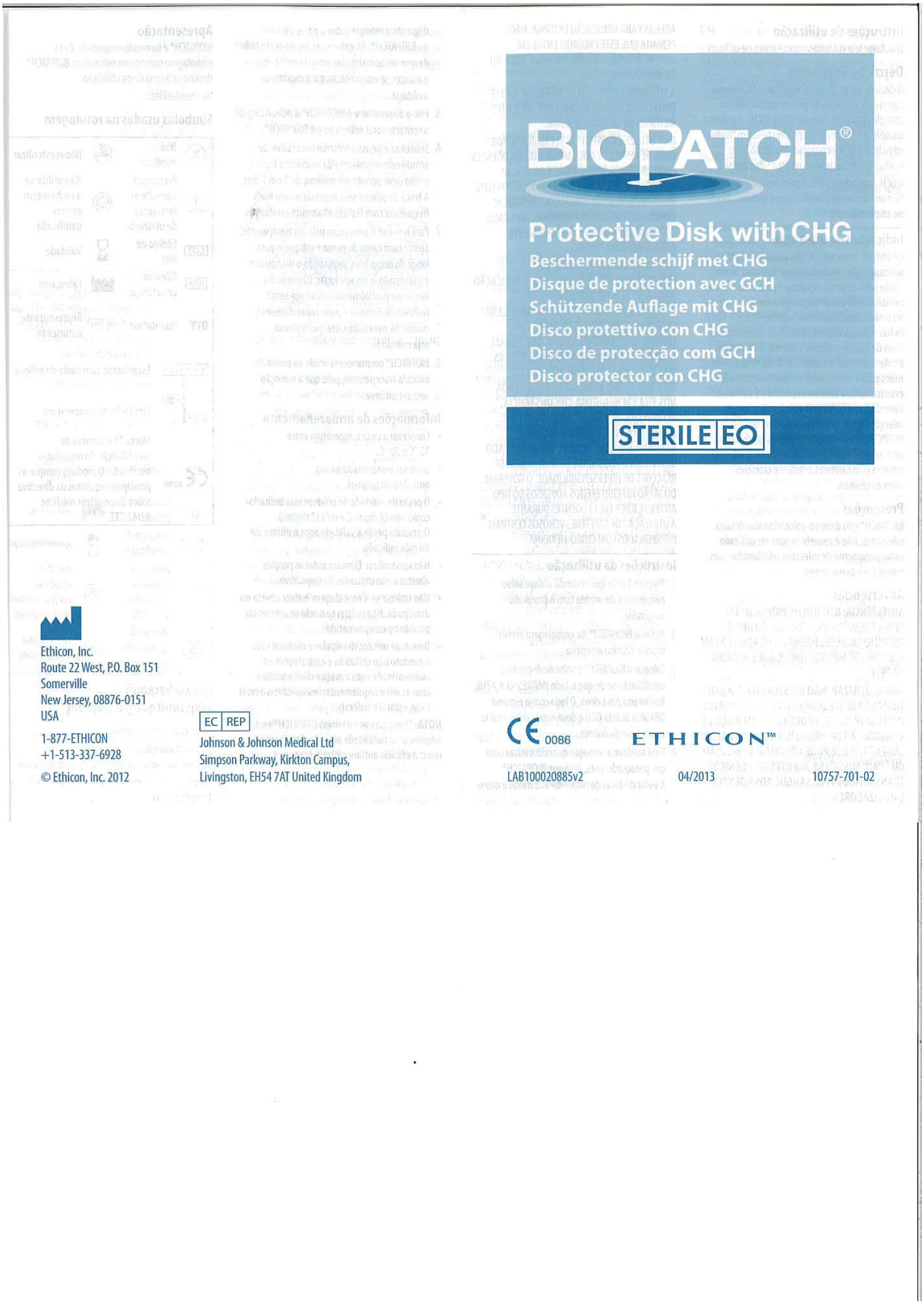
Appendix 1 Study Schedule

Appendix 2 Package Insert

Appendix 1: Visit Schedule

Visit number	Week of study
1	2
2	6
3	12
4	24
5	36
6	52

Appendix 2: Package Insert



Instructions For Use

(Please Read Carefully Before Using)

Product Description

BIOPATCH® Protective Disk with CHG is a hydrophilic polyurethane absorptive foam with Chlorhexidine Gluconate (CHG). The foam material absorbs up to eight times its own weight in fluid, while the CHG incorporated into the dressing inhibits bacterial growth under the dressing.

Chlorhexidine Gluconate is a well-known antiseptic agent with broad-spectrum antimicrobial and antifungal activity.

Indication For Use

BIOPATCH® containing Chlorhexidine Gluconate is intended for use as a hydrophilic wound dressing that is used to absorb exudate and to cover a wound caused by the use of vascular and non-vascular percutaneous medical devices such as: IV catheters, central venous lines, arterial catheters, dialysis catheters, peripherally inserted coronary catheters, mid-line catheters, drains, chest tubes, externally placed orthopedic pins, and epidural catheters. It is also intended to reduce local infections, catheter-related blood stream infections (CRBSI), and skin colonization of microorganisms commonly related to CRBSI, in patients with central venous or arterial catheters.

Precautions

BIOPATCH® should not be placed over infected wounds. It is not intended to be used as a treatment of percutaneous device-related infections.

Warnings

WARNING: DO NOT USE BIOPATCH® ON PREMATURE INFANTS. USE OF THIS PRODUCT ON PREMATURE INFANTS HAS RESULTED IN HYPERSENSITIVITY REACTIONS AND NECROSIS OF THE SKIN.

DO NOT RESTERILIZE/REUSE. REUSE OF THIS DEVICE (OR PORTIONS OF THIS DEVICE) MAY CREATE A RISK OF PRODUCT DEGRADATION AND CROSS-CONTAMINATION, WHICH MAY LEAD TO INFECTION OR TRANSMISSION OF BLOOD-BORNE PATHOGENS TO PATIENTS AND USERS.

FOR EXTERNAL USE ONLY. DO NOT ALLOW THIS PRODUCT TO CONTACT THE EYES, EARS, MOUTH, OR MUCOUS MEMBRANES.

THE SAFETY AND EFFECTIVENESS OF BIOPATCH® HAS NOT BEEN ESTABLISHED IN CHILDREN UNDER 16 YEARS OF AGE.

DO NOT USE BIOPATCH® DIRECTLY OVER BURN INJURY OR ON PATIENTS WITH A KNOWN SENSITIVITY TO CHLORHEXIDINE GLUCONATE. ADVERSE REACTIONS TO CHLORHEXIDINE GLUCONATE SUCH AS DERMATITIS, HYPERSENSITIVITY, AND GENERALIZED ALLERGIC REACTIONS ARE VERY RARE, BUT IF ANY SUCH REACTIONS OCCUR, DISCONTINUE USE OF THE DRESSING IMMEDIATELY.

HYPERSENSITIVITY REACTIONS ASSOCIATED WITH THE TOPICAL USE OF CHLORHEXIDINE GLUCONATE HAVE BEEN REPORTED IN SEVERAL COUNTRIES. THE MOST SERIOUS REACTIONS [INCLUDING ANAPHYLAXIS] HAVE OCCURRED IN PATIENTS TREATED WITH LUBRICANTS CONTAINING CHLORHEXIDINE GLUCONATE, WHICH WERE USED DURING URINARY TRACT PROCEDURES. PREPARATIONS OF THIS TYPE ARE NOT APPROVED FOR SALE IN THE U.S. UNDER ANY CIRCUMSTANCES. CAUTION SHOULD BE USED WHEN USING CHLORHEXIDINE-CONTAINING PREPARATIONS AND THE PATIENT SHOULD BE OBSERVED FOR THE POSSIBILITY OF HYPERSENSITIVITY REACTIONS. THE GOVERNMENT OF JAPAN HAS REPORTED ANAPHYLACTOID-TYPE ADVERSE EVENTS IN 13 PATIENTS WHILE USING CENTRAL VENOUS CATHETERS IMPREGNATED WITH CHLORHEXIDINE.

Directions For Use

1. Prepare the skin surrounding the percutaneous device according to hospital protocol.
2. Remove BIOPATCH® from the sterile package using aseptic technique.
3. Place BIOPATCH® around the device, making sure the BLUE PRINTED side is facing upward. The WHITE foam side releases the Chlorhexidine Gluconate (CHG) and should be in contact with the patient's skin.
4. In order to ensure easy removal when used with a film dressing, place BIOPATCH® around the device site in such a way that the device rests upon the slit portion of the BIOPATCH®. The edges of the radial slit must be pushed together and remain in contact to maximize efficacy.
5. Secure the device and BIOPATCH® to the skin. Ensure complete contact between the skin and BIOPATCH®.
6. Change the patch as necessary, in accordance with facility protocol; dressing changes should occur at a minimum of every 7 days. Dressing changes will be needed more frequently with highly exuding wounds.
7. To remove the transparent film dressing, pick up the corner of the dressing and stretch the dressing away from the device, holding the device in place. (Dressing will partially lift.) Peel back until resistance is felt. Repeatedly stretch and peel as necessary until the dressing is removed.
8. BIOPATCH® will remain attached to the transparent film dressing, so removal will be simultaneous.

Storage Information

- Store between 15°C and 30°C (59°F and 86°F).
- It is to be stored in its original packaging.
- Expiration date of the product is indicated as year (4 digits) and month (2 digits). The product expires after the last day of the month indicated.
- Do not resterilize. Discard all open and unused portions of the device.
- Do not use if the package is opened or damaged. Do not use if seal is broken or compromised.
- After use, handle and dispose of all unused product and packaging in accordance with accepted medical practice and applicable local, state, and federal laws and regulations.

NOTE: Over time, the BIOPATCH® may turn yellow in color. This coloration does not reduce the antimicrobial efficacy of the dressing.

How Supplied

BIOPATCH® is supplied sterile. Each package contains a single disk. BIOPATCH® is intended for single use only.

Do not resterilize.

Labeling Symbols

	Do not reuse		Do not resterilize
	Caution! See instructions for use		Do not use if package is damaged
LOT	Batch code		Use by
REF	Catalogue number		Manufacturer
QTY	Quantity	EC REP	Authorized representative
STERILE EO	Sterilized using ethylene oxide		
59°F 15°C / 86°F 30°C	Temperature limitation		
CE 0086	CE-Mark and Identification Number of Notified Body. The product meets the essential requirements of Medical Device Directive 93/42/EEC.		