Research Protocol IRB # 18-0132

Title:

Induction of labor in women with unfavorable cervix: randomized controlled trial comparing outpatient to inpatient cervical ripening using Dilapan-S® (HOMECARE)

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1. Introduction and Purpose

Historically, mechanical methods were the first methods developed to ripen the cervix or to induce labor (1). Dilapan-S®, a hygroscopic cervical dilator made of a patented hydrogel (AQUACRYL), works by absorbing fluid from the cells of the cervical canal, resulting in reversible cell wall dehydration and softening. The increase in volume of the rod(s) in turn, leads by mechanical stretch, to endogenous PG release with resultant cervical ripening. Dilapan-S® is approved by the FDA for cervical ripening in the third trimester. Recently a non-inferiority randomized trial at our center comparing Dilapan-S® to the most commonly used, but not FDA approved, mechanical dilator method (Foley balloon) was completed and results show that it is not inferior to the latter (https://clinicaltrials.gov/ct2/show/NCT02899689). The usual practice with mechanical ripening methods is to insert the mechanical dilator in the hospital and then await cervical ripening, which can take up to 12 hours. We believe that allowing the subject to go back home after insertion is a promising strategy that lowers in-hospital healthcare costs and improves subject satisfaction. Therefore, we propose a randomized controlled trial to compare the efficacy and safety of outpatient versus inpatient pre-induction cervical ripening with Dilapan-S® in pregnant women greater than 37 weeks.

2. Background

Labor induction is a common obstetric procedure that is generally undertaken when the risks of continuing pregnancy outweigh the benefits (2). To maximize the success of induction of labor in women with an unfavorable cervix, various ripening methods are available. These include pharmacological agents such as prostaglandins and mechanical agents such as the Foley balloon cervical dilator, which has been used in labor delivery units for decades. Mechanical methods of labor induction are safe and cost effective. Recently, Dilapan-S® was approved by the FDA as another form of mechanical dilators. The rates of labor induction continue to increase and a recently completed trial which showed that induction at 39 weeks decreases cesarean delivery compared with expectant management is expected to lead to even higher rates of induction (2). Currently, cervical ripening in the US is performed as inpatient. A few pilot studies and the mechanism of action of mechanical dilators support the safety of allowing women to go home after insertion. There have been multiple proposals to study outpatient cervical ripening (3-7), but none evaluated the role of Dilapan-S® in the outpatient setting. Unlike the Foley balloon, Dilapan-S® is FDA approved for labor induction and does not have any parts that protrude from the vagina, making it the ideal candidate for outpatient cervical ripening. However, data are lacking regarding the comparative effectiveness of inpatient versus outpatient Dilapan-S® in labor induction. Trials are also needed to determine whether outpatient cervical ripening actually shortens length of hospital stay compared with inpatient cervical ripening.

3. Concise Summary of Project

The **target population** for our study is women who present for induction of labor. If there is a decision by the obstetrical team to place a mechanical dilator for cervical ripening, the obstetrical team will notify the research staff so that the patient may be screened for the study. If the subject is eligible for the trial, written informed consent will be obtained by person-to-person contact. The PI, study coordinator, or a collaborator will be responsible for the informed consent procedure. After informed consent is obtained and Dilapan-S® is placed, the patient will be randomized to the Outpatient or the Inpatient group. Those randomized to the outpatient group will be asked to come back within 12 hours or sooner if contractions or other conditions arise.

Our **primary objective** will be to compare the hospital length of stay in the inpatient setting to the outpatient setting.

Secondary objectives will be to compare other clinical outcomes such as composite maternal and neonatal outcomes, vaginal delivery rate within 24 and 36 hours after admission, time to reach active stage of labor defined as ≥ 6 cm, change in Bishop score, rates of spontaneous and operative vaginal delivery, rate of cesarean delivery, adverse events, healthcare cost impact and subject satisfaction.

Healthcare cost impact will be assessed based on direct hospital costs or Medicaid charges, using cost minimization technique. In cost-minimization analysis, two or more interventions that have been assumed or shown to have the same effectiveness are compared for cost and the least expensive one is recommended from an economic perspective. The primary analysis will be performed for all those randomized including the costs/charges after randomization. A secondary analysis will be performed accounting separately for costs/charges before randomization.

Secondary Analysis/ Metanalysis will be performed for all those randomized as individual participant data meta-analysis all data from respective randomized controlled trials in the different centers, including from UTMB, will be de-identified. All centers will be requested to send the raw data for secondary analysis in an individual participant data meta-analysis. Research groups who share data will get the opportunity of a co-authorship in relation to the size of their study.

Data will be shared in a file that is encrypted and deidentified and password protected.

Randomization will be performed using a computer-generated random list of numbers assigning subjects to the 2 groups of the study. This list of random number assignments will be kept secure in an opaque envelope until the end of the study. 2 randomization sequences will be required for UTMB and CUMC sites.

No significant adverse effects are expected with the use of Dilapan-S® for mechanical dilation as an outpatient when compared to inpatient setting. The most common adverse events from cervical ripening with mechanical dilators such as the Foley balloon have been reported to be less than 1% (8), the most common being pain (0.26%), unintended amniotomy (0.04%), vaginal bleeding (0.07%), non-reassuring fetal heart tracing (0.07%), and uterine tachysystole (too low to quantify). Our group also reported the following adverse effects with inpatient use of Dilapan-S® for cervical ripening in a group of 444 subjects (9):

Maternal and neonatal adverse events	Nr. of cases (%)	Comments (n)
Uterine tachysystole	1 (0.2)	
Non reassuring fetal heart rate	1 (0.2)	
Maternal complications/discomfort	15 (3.4)	Bleeding during insertion/extraction of dilators (12), Cramping/pain (1), Other (1)
Uterine contractions	111 (25)	Tocography during cervical ripening showed low frequency and mild intensity contractions
Maternal infection	14 (3.2)	Chorioamnionitis (9), Urinary tract infection (3), Endomyometritis (1), Wound infection (1)

NICU admission	6 (1.4)	Meconium aspiration (2), Growth restriction (2), Asphyxia (1), Congenital cardiac abnormality (1)
Neonatal infection	1 (0.2)	Neonatal sepsis (maternal group B Streptococcus was not observed prior IOL)

The most significant potential risks noted with Dilapan-S® occur during or shortly after insertion and include vaginal bleeding due to cervical trauma and incidental rupture of membranes, as well as pain or discomfort with placement. If these occur and are persistent (i.e. unresolved pain despite analgesia), subjects will be admitted for delivery (as they require maternal monitoring) and will not be randomized, since they do not fulfill the eligibility criteria to receive the outpatient intervention.

Similarly, in the case of inability to place Dilapan-S®, patients will not be randomized and will be considered a screening failure (please refer to section 4.7 for further details). Recent data reports that the risks associated with outpatient pre-induction are similar when compared to inpatient pre-induction cervical ripening (10).

The study period will be between September 2018 and December 2021. The sample size will be up to 376 consented subjects at UTMB and at CUMC (see section 12).

The subject will be withdrawn from the study at any time, if she wishes to discontinue participation and withdraw her consent (refer to section 4.7 for details).

The data collected will be kept on a password-secured UTMB or CUMC computer. An encrypted USB flash drive will be used to transfer data, if needed. The data will be linked to the patient by the patient's MRN number. This identifier is needed to access and analyze demographic data. After analysis of the data, all identifiers will be deleted.

Data to be collected will consist of maternal age and ethnicity, gravida/para, gestational age, height, weight, estimated fetal weight, reason for induction, date and time of device placement, date and time of delivery, mode of delivery, Bishop score at eligibility assessment, Bishop score prior to dilator insertion, Bishop score after removal or expulsion of dilator, date and time of rupture of membranes, date and time of device expulsion/removal, hospital length of stay, other intrapartum and obstetrical interventions, complications in device placement and cervical ripening, during labor and delivery including but not limited to meconium, infections, hemorrhage, fetal decelerations and subject satisfaction. We will also collect the amount of analgesics subjects received during device placement, cervical ripening and induction time (includes acetaminophen or intravenous medications or regional anesthesia). Data will be abstracted from the medical records as well as from direct interview. We will also collect basic neonatal data including birth weight, Apgar scores, rate of admission to neonatal intensive care unit, infections, and other neonatal complications. The data collected will not be used for clinical diagnosis or treatment purposes. Additional economic data to be collected includes the following admission direct costs or charges from the following services/departments: Blood Bank Transfusion Operations, Chemistry Division, Hematopathology Division, JSH Labor & Delivery unit, Materials Management, Microbiology Division, Mother Baby Unit, Pharmacy, Respiratory Care Services, Surgical Operating Suite.

4. Participating sites:

The following sites are participating in this trial:

The University of Texas Medical Branch (UTMB) site:
301 University Blvd.
Galveston TX, 77555
UTMB is the leading site for this trial. There is no specific accrual number per site. Across multi-sites, randomization is centralized by sponsor.

Columbia University Medical Center (CUMC) site. The study will be conducted on 2 clinics listed below:
Clinic 1: Allen Hospital
5141 Broadway, New York, NY 10034

Clinic 2: Lawrence Hospital
55 Palmer Ave, Bronxville NY 10708
Contact: Dr. Rachana Gavara, PI rg2460@cumc.columbia.edu

Each site will be having the protocol reviewed and approved independently by their local IRB before participating in this trial or recruiting.

5. Study Procedures

VISIT #1

5.1. Screening, eligibility assessment, consenting and baseline data collection

After institutional review board (IRB) approval, pregnant women who have a plan of care for induction of labor at term will be approached by the principal investigator or any of the co-investigators for participation in the study. Informed consent for this study can be obtained during several different phases of interaction with the patient:
Phase 1: At any antenatal obstetrical office visit when decision is made to schedule subject for induction of labor.
Phase 2: Potential subjects presenting for induction of labor at term in the "Labor and delivery" unit (L&D).
Subjects willing to participate in the study will be evaluated for their eligibility including their Bishop score. The latter will be obtained from the medical record after the initial pelvic exam which is standard of care in our unit. Subjects will be reassured that participation in the study is voluntary and will not interfere with diagnosis or treatment of her condition. The subjects will receive the same care and expertise as any other subject treated in our unit. Subjects are approached in a private patient room, and written consent will be obtained by direct person-to-person contact. The principal investigator, study coordinator, or a collaborator will be responsible for the informed consent. Non-English-speaking subjects are anticipated to be part of the study population and informed consent will be provided in their primary language. We will also be using the teach back method; briefly the potential subject will be asked to explain in their own words what they need to know or do, we will also ensure they understand the study and, whenever needed, re-explain to them about the study procedures and risk of participating in the trial. After obtaining informed consent, and Dilapan-S® is successfully placed (see section 4.2) and after 30 minutes period of observation, subjects who remain eligible will be randomized to management as inpatient versus outpatient (see section 4.3).

5.2. Placement of synthetic osmotic cervical dilator

Placement of the Dilapan-S® will be performed by trained medical personnel. After informed consent is obtained, Dilapan-S® will be placed as follows:
Before the device placement, subjects will undergo continuous cardiotocography (CTG) monitoring for 30 minutes while fetal condition and uterine activity are monitored. The cervix is visualized with a sterile vaginal speculum and cleaned with iodine or chlorohexidine. As many synthetic osmotic cervical dilators (Dilapan-S®, Medicem Technology s.r.o., Kamenne Zehrovice, Czech Republic) as possible are inserted into the cervical canal under direct visualization. Synthetic osmotic dilators are inserted into the cervical canal with special attention to cross through the internal os.
The number of Dilapan-S® rods inserted will vary, depending on the status of the cervix for the particular subject. Synthetic osmotic dilators will be inserted as per manufacturer's instructions (IFU –

Appendix 1). After insertion, the subject will be evaluated for excessive bleeding, pain or other concerns by the clinical providers (see section 4.4). The synthetic osmotic dilators will be left in place for at least 12 hours, and no longer than 24 hours. Subjects will be instructed, that under no circumstances they should try to remove Dilapan-S® themselves. If subject removes the device herself, such act will constitute protocol deviation and the subject will be assessed for cervical ripening within Intent-to-Treat analysis (see section 4.4 for details) but will not be included in the Per-Protocol-Population analysis.

In the rare event that the Dilapan-S® cannot be inserted or contraindications for outpatient management develop during insertion or during the observation period after the insertion but before randomization (subject changed her mind and desires to stay inpatient, significant vaginal bleeding during insertion, non-reassuring fetal heart rate, rupture of membrane, intractable pain or other concerns the providers or investigators feel that patient cannot be managed as an outpatient), then the subject will not be randomized nor included in the analyses. These subjects will be considered as screening failures and managed as inpatient according to standard practice and under the direction of the clinical team. Refer to section 4.8.1 for further details.

5.3. Randomization

After Dilapan-S® placement, and if the subject remains eligible, subject will be randomized to the outpatient group or the inpatient group. A confidential computer-generated simple randomization scheme will be prepared and provided by independent vendor (PharmTest, s.r.o., Czech Republic) to our study coordinator. The currently used randomization code will be replaced by 2 randomization codes, 1 of them for CUMC site (both clinics will use the same randomization sequence. The randomization envelopes to be use at CUMC will be provided by UTMB).
A randomization log with group assignment, subject name, and medical record *number* will be used to track the randomization process. The subject will be included in the analysis by intent-to-treat once the randomization assignment has been made.

5.4. Pre-Induction

5.4.1. Group Assigned to Outpatient Cervical Ripening

After Dilapan-S® placement, subject will be monitored for at least 30 minutes. If no contraindications, such as tachysystole, active vaginal bleeding, rupture of membranes or nonreassuring fetal testing (defined as minimal or absent variability, abnormal baseline, or presence of decelerations) evidence of labor, or other serious medical conditions deemed by the clinical staff or the attending physician to preclude outpatient cervical ripening develop after insertion, the subjects will be randomized. After randomization subject will record the pain she experienced during insertion in the patient's survey (see Appendix 3). Those subjects randomized to outpatient ripening will be given the option to either stay in a hotel or, if they are able to reach the hospital within 60 minutes, return home. The cost for the hotel will be covered by the study budget. Subjects at CUMC will solely be given the option to stay at home. Subjects will be allowed to ambulate, shower and perform regular activity during that period. "Nothing per vagina" will be allowed (incl. intercourse, tampons etc.). Subjects will also be instructed to return to L&D unit 12 hours after insertion, or earlier if any excessive bleeding, rupture of membranes, pain or other concerns (contractions, decreased fetal movement) develop before the 12 hours. Special leaflet (Appendix 2) will be provided to subjects leaving the hospital, with detailed instruction, emergency contacts to appropriate study/clinical staff and space to document of oral medication taken for pain relief (acetaminophen). Subject will also document the date and time of membrane rupture if applicable.

Reasons for examining or removing dilators earlier include but are not limited to:

1) Spontaneous onset of labor
   (defined as regular, firm, uterine contractions with an effaced cervix >80% and a cervical dilatation > 3 cm)
2) Other than category I fetal heart rate tracing
   (category I includes all: Baseline rate: 110–160 beats per minute, baseline FHR variability: moderate, absent late or variable decelerations, Early decelerations: present or absent and accelerations: present or absent)
3) Spontaneous rupture of membranes or need for amniotomy
4) Spontaneous expulsion of Dilapan-S® rods
5) Subject removed the rods herself

After the designated 12 hours' time or earlier, if indicated, subjects are to return and to be admitted to L&D unit for standard protocol of labor induction. If the cervix remains unfavorable after extraction or spontaneous expulsion of the dilators (< 3cm and at most 60% effaced), additional mechanical or pharmacological cervical ripening may be provided at the provider's discretion. The agent/type will be recorded into the data sheet.
If subject does not return in the designated time and date as instructed (12 hours window), all attempts will be made to contact the subject by phone or supporting contact person. Subject will also be instructed that if she presents to another hospital, she needs to inform the clinical staff seeing her that she is participating in a trial and that Dilapan-S® was placed for cervical ripening, and to present the study card. We will also do our best to obtain our primary outcome through release of records.

5.4.2. Group Assigned to Inpatient Cervical Ripening

Subjects randomized to inpatient management will be admitted to L&D unit and standard clinical protocol will be initiated for cervical ripening and labor induction. During the period of 12 hours of cervical ripening subject is to remain "nothing per vagina" and undergo continuous fetal heart rate monitoring. During this period, clinical care will be left to the provider's discretion (standard of care at the institution) including "nil per os" or "nothing per os" (NPO) status. No other interventions are to occur during this period of 12 hours, unless clinically indicated. Reasons to remove the dilators and management after 12 hours will be the same as for the outpatient group (see sec. 4.4.1.).

VISIT #2

5.5. Labor Induction and Labor

Management of the subject after the initial 12 hours of pre-induction or following the earlier removal or spontaneous expulsion of the dilator will be the same for both groups and at the discretion of the clinical team. Additional ripening (mechanical or prostaglandins) and/or oxytocin may or may not be needed. If needed, duration, type and dose of additional ripening agents and oxytocin will be documented.

Routine intrapartum care will be provided and relevant data collected by the subject's managing obstetrical team.

Trained and experienced research staff will be responsible for all research data abstraction.
The PI and collaborators will review and validate the outcomes. If there is uncertainty, a second investigator will review the chart, discuss with the other investigators as needed, and make a final determination regarding the outcome.

Subjective assessment data will be collected, using adequate validated tools either after Dilapan-S® extraction or any time prior labor or post-partum (Appendix 3) at the time point best suitable for both the subject and the study team.

5.6. Post-partum data collection

Maternal and neonatal outcomes will be assessed following delivery, as detailed in section 5.
Subjects will be encouraged to call the research team with any concerns.
Data collection forms will be used during these processes and charts will be reviewed.
Subjects' direct participation will end after her discharge home from the hospital, however, data on postpartum infections or hospital readmission will be collected from medical charts 2 weeks after subject's delivery.

5.7. Follow-up

No extra postpartum follow-up visits will be performed. Neonatal and maternal outcomes will be collected up to two weeks postpartum and documented in the relevant data collection forms. If these outcomes are not obtainable by chart review, all attempts will be made to obtain relevant outcomes from subject by phone. These will be reported as missing data, if unable to be reached by four weeks after delivery.

5.8. Premature Terminations

5.8.1 Screening failure

A subject who is screened and consented, but Dilapan-S® isn't placed will be considered a screen failure.

5.8.2 Early (or premature) termination

A study subject will be discontinued from participation in the study if any of the following occurs:

- Medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the treating investigator.
- Subject wishes to end her study participation prematurely for any reason.
- Lost to follow-up before reaching primary outcome (e.g. did not return from outpatient ripening).

5.8.3 Rules for consent withdrawal

If a subject withdraws her consent to participate in the study, all efforts will be made to discuss with the subject that despite the withdrawal, as many data as possible will be collected, such as safety data, AEs, SAEs. In such circumstances or situations, no data will be collected from the moment of her consent withdrawal, however, data collected before the withdrawal will be kept.

The subject can still request the deletion of such data at any time, but the subject will need to request it in written for proper documentation.

Subjects who will either withdraw their consent or end their participation in the study prematurely will not be replaced. Data obtained will be assessed within ITT population analysis.

6. Study Outcomes

6.1. Primary Outcomes

Rate of hospital stay longer than 48 hours (from admission to discharge)

6.2. Secondary Outcomes

- Rate of vaginal deliveries (%)
- Rate of vaginal deliveries within 24 hours since admission to hospital (%)
- Rate of vaginal deliveries within 36 hours since admission to hospital (%)
- Time from hospital admission to reach active stage of labor defined as ≥ 6 cm (mins)
- Time from device placement to reach active stage of labor defined as ≥ 6 cm (mins)

- Change in Bishop score from insertion to extraction of device
- Change in cervical dilation after Dilapan-S®
- Rate of spontaneous vaginal deliveries after one round of cervical ripening (%) (no additional medical or mechanical interventions)
- Rate of operative vaginal deliveries (%)
- Rate of caesarean deliveries (%)
- Rate of artificial rupture of membranes (AROM) (%)
- Rate of epidural analgesia (%)
- Total duration of Dilapan-S® application (insertion to removal/extraction) (mins)
- Device placement to delivery interval (mins)
- Induction (Oxytocin/Prostaglandin initiation) to delivery interval (mins)
- Analgesia used during device placement (%), cervical ripening (%) and labor induction (%)
- Rate of adverse neonatal outcomes (composite and individual) –Apgar score <7 at 1-5-10 minutes, Cord arterial pH <7.1, neonatal ICU admission (%)
- Occurrence of maternal and neonatal complications within 2 weeks after delivery (%)
- Total duration of maternal hospital stay (hours)
- Subject reported clinical outcomes (sleep, rest, pain, activities of daily living, etc.) (Appendix 3)
- Subject reported satisfaction with Dilapan-S® treatment (Appendix 3)
- Medicaid charges for each hospitalized subject in both arms
  (Blood Bank Transfusion Operations, Chemistry Division, Hematopathology Division, JSH Labor & Delivery unit, Materials Management, Microbiology Division, Mother Baby Unit, Pharmacy, Respiratory Care Services, Surgical Operating Suite)

7. Inclusion and Exclusion Criteria

7.1. Criteria for Inclusion of Subjects:

Subjects must meet all of the inclusion criteria in order to be eligible to participate in the study.
Inclusion criteria are:

1. Pregnant woman whose plan of care is induction of labor
2. Maternal age between 18 and 45 years
3. Understanding and capable to sign informed consent
4. Singleton pregnancy
5. Gestational age $\geq 37^{0/7}$ weeks
   (based on a sure last menstrual period or a first trimester dating ultrasound)
6. Live fetus in cephalic presentation
7. Intact membranes
8. Pelvic exam (sterile vaginal exam) of less than or equal to 3cm and at most 60% effaced

7.2. Criteria for Exclusion of Subjects

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.
Exclusion Criteria are:

1. Active labor
2. Active genital herpes
3. Chorioamnionitis
4. Transfundal uterine or cervical surgery
5. Previous cesarean delivery

6. Non-reassuring fetal status
7. Need for continuous maternal or fetal monitoring during ripening
8. Contraindication for vaginal delivery
9. Active vaginal bleeding
10. Abnormal placental location or adherence (placenta previa or unresolved low lying placenta)
11. Estimated fetal weight > 5000 g (non diabetic) or > 4500 g (diabetic)
12. Intrauterine growth restriction (estimated fetal weight <10 percentile)
13. Oligohydramnios (amniotic fluid index < 5cm or deep vertical pocket of < 2 cm)
14. Fetal anomaly
15. Need for inpatient care (e.g. hypertension, insulin-dependent diabetes)
16. Poor or no access to a telephone and cannot be placed in the hotel
17. Absence of support person (no adult accompanying the subject during outpatient cervical ripening period)

8. Sources of Research Data

Medical chart/records, charges for Medicaid services report forms and direct cost reports will be used as source for data collection.

9. Potential Risks

9.1. Randomization risk

Since the location of pre-induction management will be randomized, it is possible that the subject may be in a group with higher adverse outcomes.

9.2. Loss of Confidentiality

Any time information is collected, there is a potential risk for loss of confidentiality. Every effort will be made to keep subject's information confidential; however, this cannot be guaranteed.

9.3. Risks associated with mechanical dilator

- Vaginal bleeding during/after device insertion
- Subjective pain felt during insertion
- Vaso-vagal reaction from manipulation of the cervix
- Contamination of the device during insertion
- Allergic reaction from hypersensitivity to the components
- Rupture of membranes
- Uterine tachysystole (> 5 contractions in 10 mins averaged over 30)
- Cervical trauma during insertion or extraction.
- Retraction of the device into the uterine cavity
- Entrapment of the device
- Fragmentation of the device

10. Subject Safety and Data Monitoring

10.1. Safety reporting

Scope

In relation to Dilapan-S®, the Clinical Trial is a post-market clinical follow-up study (PMCF) conducted using CE marked device ("Conformité Européenne") within its intended use. The provisions of Directive 93/42/EEC concerning information and notification of incidents occurring following placing devices on the market are fully applicable. Medical Device Reporting regulation (21 CFR 803) will be followed to report certain device related adverse events and product problems to the FDA.
The Investigator shall ensure that Sponsor will be informed about any adverse events (AEs) that would be related to study device according to the definitions given below. Complaints about any product problem are within the scope of obligatory notification too, including product defects, malfunctions or user errors.
AEs not related to the study device are not to be reported to sponsor. Borderline events should be handled conservatively and the sponsor should be notified in case of any doubt.

Definitions

Adverse Event (AE) is any untoward medical occurrence in a subject and that does not necessarily have a causal relationship to the study device and surgical procedure.

Serious Adverse Event (SAE) is any AE that:

- Results in death.
- Is life-threatening.
- Leads to hospitalization or prolongation of hospitalization.
- Causes disability and/or permanent impairment of a body function or structure.

- Requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.
- Leads to fetal demise, a congenital abnormality, or birth defect.

Product Problem includes:
- Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. It also includes inadequate labelling.
- Malfunction: failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan.
- User error: act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Evaluation of an AE
When evaluating AEs, the Investigator must determine:
- if the event is serious. Seriousness criteria are based on definition of an SAE (above).
- if the event is related to the study device. The following rules are to be applied:
  a) Not Related: AE which are clearly and incontrovertibly due to causes other than the study device (e.g., concomitant disease).
  b) Related: AE which are felt with a reasonable degree of certainty to be related to the study device.
  c) Unknown: AEs for which a connection with the study device cannot be ruled-out with certainty, or not enough information is available to assess the relationship.

Reporting
The collection of AEs begins at the time the subject is enrolled into the study (eligible subject with signed informed consent).
Reporting will be done in written via the attached Safety Report Form (Appendix 4).
The Investigator is obligated to send the applicable report to the Sponsor within 24 hours of becoming aware of the event to ensure the safety of all participants in the study and to meet regulatory reporting requirements.
Subsequent reporting to the IRB and the corresponding regulatory authorities will be organized by the Sponsor and in accordance with all applicable legal requirements of the concerned country.

10.2. Data Monitoring

The PI and collaborators will ensure all aspects of data quality, including monitoring for adherence to consent procedures, inclusion and exclusion criteria, valid abstraction, correct entry, timeliness and responsiveness to data queries.
Data will be collected and stored with the participant ID code only. The master enrollment log linking subject identifiers with study ID numbers will be kept in a password-protected database on the OB/GYN department's internal server separate from the data. Data collection forms will be used. Data on these forms devoid of personal identifiers will be securely stored at our perinatal research division. The research coordinator will be available to monitor the data and correct any discrepancies based on source documents if needed.

Data quality and safety of subjects will be monitored also by sponsor's representative to assure independent review. Any issue identified will be followed up closely to assure the subjects' safety and adherence to protocol as well as data quality.

The sponsor's monitor performs monitoring remotely; therefore, they only need to formally conduct in person monitoring visits to review the informed consents and other paper documents. One monitoring visit for approximately every 60 randomized subjects is sufficient. The monitoring visit frequency depends on enrollment, if enrollment increases, the frequency will increase as well. In conclusion, we expect approximately 2-4 monitoring visits per year.

11. Procedures to Maintain Confidentiality

Each subject will be assigned a study number (Subject ID) with personally identifiable information deleted or removed. This Subject ID will be unique for every subject and will not contain any study group identifier. Subjects' information will be de-identified and tagged with a number. Data will be collected and stored on a UTMB or CUMC password-protected computer in a locked room.

12. Potential Benefit

This study has the potential benefit to show that outpatient pre-induction cervical ripening with Dilapan-S® decreases length of hospital stay without affecting maternal and neonatal outcomes. Ultimately, this may reduce the health care costs and workload associated with induction of labor and improve maternal neonatal early bonding.

13. Biostatistics/Sample Size

Basic principles for an evaluation of the study are presented in this section, more detailed description of how to analyze collected data will be specified in statistical analysis plan (SAP) which will be written and approved before the database lock. The statistical analysis including the data from the additional site will be specified in the SAP.

13.1. Study populations

All Randomized population

This will be comprised for all subjects who had Dilapan-S® inserted and were randomized. This includes patients who terminated participation for any reason (lost to follow-up or did not return to hospital for admission). We will perform a sensitivity analysis (worst case scenario), where we will consider these subjects to have reached the primary outcome.

Safety Population

The Safety population will be comprised of all subjects who had Dilapan-S® inserted and were randomized. This population will be used for the analysis of safety of the outpatient versus inpatient management. Subjects who were consented and had Dilapan-S® inserted, but not randomized, and had complications attributed to the device will be reported as AEs (detailed in section 9.1).

Intent-to-treat Population (ITT)

ITT includes all patients that were randomized into the study and primary outcome has been obtained. ITT subjects will be analyzed in accordance with their randomized study treatment (i.e. in the treatment group they were originally allocated, regardless of treatment actually received). ITT will be used for evaluation of the baseline characteristics and as the primary population for efficacy assessments. Other predefined subgroup interaction analysis for cervical dilation at randomization, parity (P=0 vs P>0), or BMI > 30 kg/m2 will be also performed.

Per Protocol Population (PP)

PP is a subset of ITT patients without any major protocol violation affecting the efficacy endpoints. Major protocol violations include:

1. Treatment assignment error
2. Violation of one or more inclusion/exclusion criteria
3. Use of forbidden medication
4. Premature withdrawal
5. Missing data for the evaluation of the primary endpoint

This list can be extended based on a knowledge of other serious issues appearing in the data.
PP population will be used for assessment of primary endpoint.

13.2. Analysis of primary outcome

Primary outcome of the study is the rate of hospital stay longer than 48 hours. Proportion of patients in the outpatient and inpatient group will be calculated and their difference will be tested by chi-square test by ITT analysis.

13.3. Analysis of secondary outcomes

Nominal variables will be evaluated in the same manner as the primary outcome. Continuous variables will be summarized (minimum, maximum, mean, standard deviation, median, lower and upper quartile) and the difference between groups will be tested by t-test or Wilcoxon-Mann-Whitney test as appropriate. For time-to-event outcomes, Kaplan-Meier will be used to estimate the survival curves and log-rank test will be used to test the difference between groups by ITT analysis.

13.4. Sample size

Sample size was calculated based on the determination of superiority. The primary outcome is proportion of women with hospital stay >48 hours. For the sample size calculation, we assumed the proportion in the control arm would be 54% ($p_i = 0.54$). This is based on current experience at UTMB and unpublished data from an international registry trial (9). We estimate that outpatient intervention would decrease this proportion by 30% ($p_{ii} = 0.378$). Based on 85% power and two-sided alpha of 0.05, the total sample size per group required would be 169. Accounting for 10% of premature terminations or drop outs the sample size per group becomes 188, making the total sample size needed 376.

14. Clinical Trial Registration

This trial will be registered with Clinical Trials Registry (www.clinicaltrials.gov), before recruitment is initiated after IRB approval.

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List of Appendices:

1. Instructions for Use: DILAPAN - S® Hygroscopic Cervical Dilator (*DSPIenus-Rev019/2021-04*)
2. Leaflet – instructions for patients on home-based ripening
3. Patient questionnaire
4. Safety Report Form

Appendix 1: Instructions for Use: DILAPAN - S® Hygroscopic Cervical Dilator (*DSPIenus-Rev019/2021-04*)

DILAPAN-S® Hygroscopic Cervical Dilator

Instructions for Use

GENERAL INFORMATION

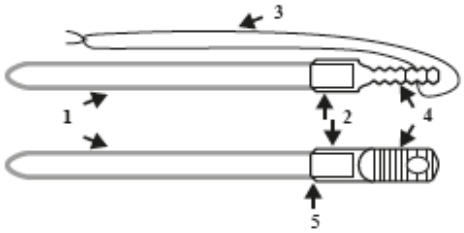
Content

A sterile hygroscopic cervical dilator packed in a printed composite primary peel-open pouch, a piece of Instructions for use.

The DILAPAN-S® is available in a box of 25 dilators and in the following dimensions: 4×65 mm, 4×55 mm, 3×55 mm.

Device description and performance

Synthetic hydrogel cervical dilator consists of the dilating part, the polypropylene handle and the marker string (see the figure below). The dilating part is manufactured from an anisotropic xerogel of AQUACRYL. The dilator is capable of increasing in diameter as it absorbs moisture from the genital tract. The marker string is tied securely to the handle of the DILAPAN-S®, and is provided to indicate its location.



1. Dilating part made of hydrogel
2. Collar
3. Marker string
4. Handle
5. Point of maximal insertion

Handling, transport, storage and waste management

Store between +15 °C and +30 °C.
Keep away from direct sunlight and high humidity.
Do not freeze.

The product, its waste materials and other consumables used during the procedure, should be disposed in accordance with local/national regulations.

Sterilization and expiration

The sterility of each device is guaranteed only when the primary packaging is unopened and undamaged.

The sterilization procedure that has been applied is marked on the label of the device – using irradiation.

INTENDED PURPOSE

Indications

The DILAPAN-S® is to be used wherever cervical softening and dilation is desired, some examples are:

- Cervical stenosis
  - Related to dysmenorrhea
  - Considered a possible cause of infertility
  - Resulting from cauterization or conization
- Placement and removal of intrauterine devices
- Induction of labor
- Radium placement
- Drainage of uterine cavity
- Endometrial biopsy
- Uterine curettage
- Suction aspiration cannula
- Operative hysteroscopy

Patient target group

The DILAPAN-S® is targeted for women indicated to labor induction or intrauterine procedure with necessary cervical ripening and/or dilation.

Intended users

The DILAPAN-S® is for use by healthcare professionals trained in obstetrics and gynecology only.

Contraindications

The DILAPAN-S® is contraindicated in the presence of clinically apparent genital tract infection.

WARNINGS

The DILAPAN-S® is intended for one-time use. Instructions for its use and handling are attached to minimize exposure to conditions that may degrade the product, patient or user.

Re-use / re-sterilization / reprocessing[1] of the DILAPAN-S® single-use medical device may result in physical damage to the medical device, failure of intended use of the medical device, and illness or injury to the patient as a result of infection, inflammation and / or disease due to product contamination, infections and insufficient sterility of the product.

[1] A process carried out on a used device in order to allow its safe reuse including cleaning.

Careful placement of the device is essential to avoid traumatic injury to the cervix or uterus and to avoid migration of the device either upward into the uterus or downward into the vagina.

The DILAPAN-S® may fragment during removal using incorrect technique. Fragmentation may result in pieces of the device being retained in the uterus. Carefully follow the Removal instructions.

Do not use if primary packaging has been opened or damaged.

Do not re-use, intended for one-time use.

Do not re-sterilize this device by any method.

Do not store at a temperature lower than +15 °C and higher than +30 °C.

Keep away from direct sunlight and high humidity.

Disposable, discard after use.

All instructions must be carefully read **prior to** using the DILAPAN-S®.

Caution: U.S. federal law restricts this device to sale by or on the order of a physician.

PRECAUTIONS

As with the use of any medical device, a careful evaluation and clinical judgement should be made by the healthcare professional before using the device for the procedure to decide on the benefit/risk ratio. Alternative treatment should be considered for patients with a pre-existing condition listed under contraindications above.

Treatment options and potential risks associated with using the DILAPAN-S® for planned procedure should be discussed with the patient before the procedure.
The patient should be instructed to report any excessive bleeding, pain, temperature elevation. The patient should be instructed to avoid bathing, douching and refrain from intercourse while the DILAPAN-S® is in place.

The patient should be instructed that it is necessary to return for removal of the DILAPAN-S® at the indicated time. Under no circumstances should the patient try to remove the DILAPAN-S® herself.

The device **should not** be left in place more than 24 hours.

When the dilator has been inserted during a procedure for termination of pregnancy, the procedure of termination of pregnancy should always be completed. Effect of termination the procedure on the fetus has not been clinically investigated.

Risks associated with the procedure

Twisting the device during its removal may cause the device to break.

In case of breakage, every attempt must be made to remove all fragments from the uterus. All fragments removed should be checked to ensure complete evacuation of the cavity. If in doubt, a hysteroscopy or ultrasound scan should be performed. The clinical effects of fragments retained in the genital tract are unknown.

Any cervical manipulation may cause a vaso-vagal reaction. The patient should be watched for evidence of any unusual pallor, nausea, vertigo or weakness. By remaining recumbent for 3 to 10 minutes these symptoms usually disappear.

Complications

The following complications may be associated with use of the DILAPAN-S® device, or may occur during the indicated procedure:

- Device entrapment
- Fragmentation or detachment of the handle
- Device expulsion
- Device retraction into the uterus
- Patient discomfort or bleeding during and/or after insertion
- Spontaneous rupture of membranes
- Spontaneous onset of labor
- Cervical laceration

USE

Examine the label of the unopened pouch and expiry date of the dilator.

Instructions for insertion

1. Insert a bivalve speculum and prepare the vagina and cervix with an antiseptic solution.
2. Remove the DILAPAN-S® from the pouch using sterile technique.
3. Moisten the DILAPAN-S® with sterile water or saline to lubricate the surface prior to insertion.
4. If necessary, use an appropriate technique to visualize the cervix and straighten the cervical canal for easier insertion of the DILAPAN-S®.

5. Insert the DILAPAN-S® in the cervical canal gradually and without undue force. It is important that the DILAPAN-S® traverses the internal os. Do not touch the dilating part with a sharp instrument.
6. Do not insert the DILAPAN-S® past the handle. The border of the collar should rest at the external os. Do not insert the DILAPAN-S® into cervix further than the arrow indicates (see the figure above – 5. Point of maximal insertion).
7. More than one DILAPAN-S® may be inserted into the cervical canal as determined to be appropriate by the physician.
8. When using several dilators, repeat steps 2 to 4. As many dilators as needed to achieve the desired effect should be inserted. Specific number of pieces always depends on decision and clinical judgement of physician and indications.
9. Insert a gauze pad moistened with sterile water or saline to help keep the DILAPAN-S® in place, if needed.

Removal instructions

1. Vaginal packing is first removed, if used during the insertion procedure.
2. Carefully remove the DILAPAN-S® by grasping the handle or pulling the string. Do not twist[2)] the DILAPAN-S® during removal. Do not grasp the collar with forceps. Do not grasp the marker string with a sharp-edged instrument[3)].

[2)] Neither grasp the collar with forceps to remove the device nor twist handle when attempting to remove the device, as this may cause the device to break.

[3)] Do not grasp the marker string with a sharp-edged instrument to remove the device, as this may cause the string to tear.

When difficulties occur during removal of the device by pulling the string, do not use excessive force on the string to remove the dilator. Use a visualization technique to identify the cause of these difficulties and remove the dilator by grasping the handle.

Occasionally, it may be necessary to use forceps to grasp the DILAPAN-S® by the handle and exert steady traction for several minutes, while the uterus is stabilized by placing an atraumatic tenaculum through the anterior lip of the cervix.

Moisten the DILAPAN-S® with sterile water or saline thoroughly during removal, if the dilator has stuck to the tissue, or more dilators have stuck together.

In very rare cases the ballooning of the inserted DILAPAN-S® above and/or below the internal cervical os has been known to cause a "tight cervix" and make for difficult DILAPAN-S® removal. This is corrected by sliding a sequence of graduated sizes of metal dilators alongside the DILAPAN-S® and through the internal os until sufficient dilation takes place to allow easy withdrawal.

If the DILAPAN-S® has somehow migrated or been placed in a false passage, it may be located using ultrasound.

NOTE: The DILAPAN-S® is not radiopaque.

INTERACTIONS

Within clinical investigations with the DILAPAN-S®, a broad range of licenced medications have been administered during indicated procedures. No specific interactions between drugs / medical devices and the DILAPAN-S® have been identified to date. Using the DILAPAN-S® does not impose any specific limitations on standard medication administered in the context of the DILAPAN-S® indications. Information provided to particular medications should be followed properly.

External influences

No negative interactions between the DILAPAN-S® and external influences were observed. Desired interference include ultrasound waves that can be used for location of the inserted dilator.

TESTING OUTCOMES

Clinical

Clinical trials have not demonstrated any allergic reactions to the device. However, an allergic reaction could result from hypersensitivity to the components.

Clinical trials have not demonstrated any infections causally related to the DILAPAN-S®. However, in the presence of pathogens, contamination of the device during insertion is possible. Administration of antibiotic for infection prophylaxis should be considered prior to insertion of DILAPAN-S®.

Mechanical

The amount of dilation achieved depends on the amount of time in situ. The following is provided as a guide.

Time in situ (hours)	Expected Dilation (in mm)	
	One DILAPAN-S® (3 mm)	One DILAPAN-S® (4 mm)
2	7.2 – 8.3	7.8 – 10.0
4	8.4 – 9.5	10.0 – 11.2
6	9.0 – 10.0	10.1 – 12.5
24	9.6 – 11.3	12.7 – 14.6

CONTACTS AND VIGILANCE

Please report incidents of death to the FDA or serious injury to your distributor (USRegulatory@medicem.com) or to the manufacturer (technology@medicem.com) in relation to the DILAPAN-S®.

Please report any potential or actual product deficiencies, and product quality issues associated with the use of the DILAPAN-S® directly to your distributor (USRegulatory@medicem.com) or to the manufacturer (technology@medicem.com).

Manufacturer:
MEDICEM Technology s.r.o.
Karlovarska trida 20, Kamenne Zehrovice
273 01, Czech Republic
Tel.: +420 317 070 370
e-mail: technology@medicem.com
http://www.medicem.com

Initial Importer, Distributor and US Agent:
Medicem Inc.
125 High Street, Suite 1704
Boston, MA 02110
Tel.: +1 973-534-2396
e-mail: USRegulatory@medicem.com

Liability

The manufacturer holds no liability for any side effects or resulting damages, losses or costs that may arise as a result of the incorrect handling or use of the device.

CE 2797

TABLE OF USED SYMBOLS

	Keep in a dry place
	Keep away from sun
	Store at 15 – 30 °C
STERILE R	Sterile, Sterilized using irradiation
	Do not re-use
°C	Degrees of Celsius
	Caution, Consult accompanying documents
	Do not resterilize
	Do not use if package is damaged
	Consult instructions for use
mm	Millimeter
LOT	Batch number
	Expiration date
	Date of manufacture
	Manufacturer
QTY	Quantity
pc / pcs	Piece(s)

Appendix 2:

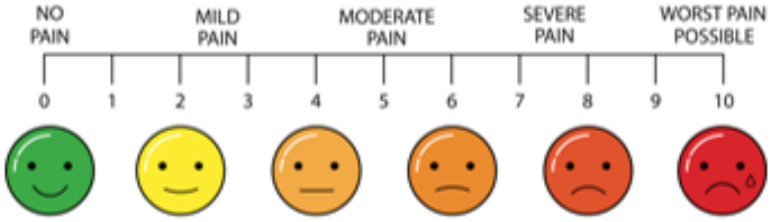
Leaflet – instructions for patients on home-based ripening

Appendix 3:
Patient Satisfaction Survey

HOMECARE Protocol # 18-0132 Subject ID: **HC –** ☐☐☐

Please think about the care you are receiving and circle the number which best indicates your agreement or disagreement with each of the following statements.

Please mark the pain level you've been experiencing during insertion of Dilapan-S.



Date: ☐☐-☐☐
Time: ☐☐:☐☐
Verified by: (initials) ☐☐

I am pleased with my overall cervical ripening experience with Dilapan-S.
(this is process when your cervix becomes soften and distended by the device inserted)

Strongly disagree				Strongly agree
1	2	3	4	5

During the cervical ripening process, I was able to sleep and to rest.

Strongly disagree				Strongly agree
1	2	3	4	5

During the cervical ripening process, I was able to walk, eat and shower.

Strongly disagree				Strongly agree
1	2	3	4	5

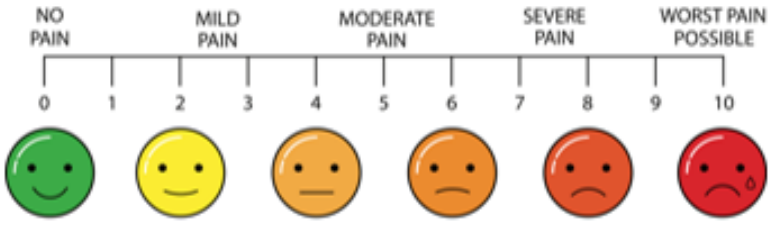
Having my cervix soften and distended in a non-hospital environment (not in the hospital) is beneficial and a great idea.

Strongly disagree				Strongly agree
1	2	3	4	5

I would choose to have my cervix soften and distended in the hospital (not at home) for my next pregnancy.

Strongly disagree				Strongly agree
1	2	3	4	5

Please mark the pain level you've been experiencing while Dilapan-S was in place.



Date: ☐☐-☐☐
Time: ☐☐:☐☐
Verified by: (initials) ☐☐

Thank you very much for taking your time to complete this questionnaire.

Appendix 4:
Safety Report Form

Research Protocol # 18-0132 **Safety Report Form**

Forward completed information to:
MEDICEM Technology, Karlovarska trida 20, 273 01 Kamenne Zehrovice, Czech Republic
e-mail: technology@medicem.com fax: +420 317 070 380

A. REPORTER (Physician, Nurse, Hospital, Other)

1. Date of this Report: *(dd-mmm-yyyy)* _ _ - _ _ _ - _ _ _ _
2. Name:
3. Address:
4. Contact e-mail:
5. Contact Phone:

B. PATIENT INFORMATION

1. Subject ID: ..... or ☐ Not Applicable
2. Year of Birth: *(yyyy)* _ _ _ _

C. ADVERSE EVENT or PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem (Device Deficiency)
2. Outcome Attributed to Adverse Event (Check all that apply)
   - ☐ Death, incl. date: _ _ - _ _ _ - _ _ _ _ *(dd-mmm-yyyy)*
   - ☐ Life-Threatening
   - ☐ Disability or Permanent Damage
   - ☐ Hospitalization (initial or prolonged)
   - ☐ Congenital Anomaly/Birth Defects
   - ☐ Required Intervention to Prevent Permanent Impairment/Damage
3. Date of Event Onset: *(dd-mmm-yyyy)* _ _ - _ _ _ - _ _ _
4. This Report is: ☐ Initial ☐ Follow-Up
5. Event or Problem Description (Narrative):
6. Other Relevant History, incl. Pre-existing Medical Conditions:
7. The Event or Problem Occurred: ☐ Before Application ☐ During Application ☐ After Application
8. Relationship to the Used Device: (*only one option to be ticked*)
   ☐ Related (probably or possibly) ☐ Not Related ☐ Not possible to determine

D. SUSPECTED MEDICAL DEVICE

1. Product Name:
2. Lot #:
3. Date of Expiration: *(dd-mmm-yyyy)* _ _ - _ _ _ - _ _ _ _
4. Date of Use: *(dd-mmm-yyyy)* _ _ - _ _ _ - _ _ _ _
5. The Suspected Medical Device is being returned: ☐ YES ☐ NO

DO NOT COMPLETE!

E. SAFETY REPORT FORM RECEIPT (to be completed by Sponsor only)

1. Date of Receipt: *(dd-mmm-yyyy)* _ _ - _ _ _ - _ _ _ _
2. Name:
3. E-mail:
4. Phone:
5. Report Reference: