DILAPAN-S

Product training

May 30th, 2017
DILAPAN-S

Product Description / Mode of Action
Introduction

- The DILAPAN-S is a synthetic hydrogel cervical dilator
- Represents 2\textsuperscript{nd} generation made of a patented hydrogel AQUACRYL.
- The rigid rod is capable of increasing in diameter by absorbing fluids from the cervical canal.

- Sterilised by irradiation.
- Supplied sterile, in peel-open packages.
- Manufactured in an ISO 9001 Certified facility.
- Fully CE Certified under the Medical Device Directive.

- Approved by FDA for sale in the United States.
- Many local registrations - Japan, Canada,..

- Available in more then 40 countries worldwide
Mode of action

The dilator increases in volume by absorbing fluids from cervical canal.

- **Mechanical:**
  - Controlled pressure on the cervical wall dilates the cervix

- **Biophysical:**
  - Partial/(reversible) osmotic cells’ dehydration softens the tissue

- **Physiological:***
  - Promotion of endogenous prostaglandins releasing causing collagen degradation and tissue restructuring

- Patented hydrogel AQUACRYL guarantees consistency of action.

- It does not contain any active substances, which could be released during its use.

* See claim „Accenturates physiological processes of labour in section Key indication / DILAPAN-S benefits
Fast acting cervical dilator

Diameter increasing

The principal effect is reached in first 4-6 hours (approximately 80% of diameter increasing).
During hydration, the length of active part is changing between -28% and +18%. The largest decrease in length occurs within 2-6 hours post-insertion. Inadequate dilatation when using the device with a 65-mm body is a less frequent occurrence. The 55mm-long dilator is suitable in cases where examination showed shortening of the cervix.
Sizes and packaging

Variety of Sizes:

- 4mm x 65mm
- 4mm x 55mm
- 3mm x 55mm

Available in boxes of 10 or 25 pcs.
History / Family of hygroscopic dilators

- **DILAPAN**
  - Represented 1\textsuperscript{st} generation of synthetic osmotic dilator
  - On the market in 80’s – 90’s last century
  - Issue: higher risk of fragmentation

- **DILAPAN-S**
  - 2\textsuperscript{nd} generation of osmotic dilator made from AQUACRYL, a patented hydrogel
  - Development initiated in 1994, fragmentation issue overcome

- **DILASOFT**
  - Made of the same hydrogel as DILAPAN-S
  - The rod is flexible and can be shaped thanks to customised production technology
  - Developed on special request of the Japanese market / sold in the Japan since 2010
  - EU launch Q1/ 2017, US, Canada, Russia as registration is completed
DILAPAN-S

Indications for use
Core indications

1. Induction of labor (IOL)

2. Cervical preparation (dilation) prior to instrumentation of the uterine cavity
   - Termination of pregnancy / induced abortion (TOP)
     • 1\textsuperscript{st} trimester
     • 2\textsuperscript{nd} trimester
     • fetal demise
   - Hysteroscopy and others

3. Cervical preparation prior to
   - Difficult embryo transfer (ART)
   - IUD (intrauterine device) insertion and extraction
DILAPAN-S

Video - intro
Maximum cervical dilation, which can be reached with 1 piece of 4mm’s rod, is (approximately):

A/ 11 mm

B/ 14 mm

C/ 18 mm
Maximum cervical dilation, which can be reached with 1 piece of 4mm’s rod, is (approximately):

A/ 11 mm

B/ 14 mm

C/ 18 mm
Explain the term „endogenous prostaglandines“.
Explain the term „endogenous prostaglandines“.

Generally, endogenous substances are those that originate from within an organism, tissue, or cell.

Endogenous prostaglandines are body own hormones, which play important role in different physiological processes. In DILAPAN-S´s indications are released from the local tissue and promote collagen fibres´ degradation and by this support softening of the cervix.
Are there other cervical dilators worldwide made of similar hydrogel AQUACRYL as DILAPAN-S.

A/ YES

B/ NO
A/ YES

B/ NO (but don’t remember DILASOFT)
Approximately 80% of rod’s swelling is reached in first:

A/ 4 hours

B/ 8 hours

C/ 10 hours

after insertion.
Approximately 80% of rod’s swelling is reached in first:

**A/ 4 hours**

B/ 8 hours

C/ 10 hours

after insertion.
When swelling, the rod is usually getting shorter by:

A/ 10%
B/ 20%
C/ 50%
D/ length remains the same
When swelling, the rod is usually getting shorter by:

A/ 5%

B/ 20%

C/ 50%

D/ length remains the same
Quiz / part 1
Question 6

Mark correct combination of available sizes:

A/ 3 x 45mm, 3 x 55mm, 4 x 55mm

B/ 3 x 50mm, 4 x 55mm, 4 x 65mm

C/ 3 x 55mm, 4 x 55mm, 4 x 65mm
Mark correct combination of available sizes:

A/ 3 x 45mm, 3 x 55mm, 4 x 55mm

B/ 3 x 50mm, 4 x 55mm, 4 x 65mm

C/ 3 x 55mm, 4 x 55mm, 4 x 65mm
During insertion, active medical substance is released from the rod to support cervical ripening/dilation.

A/ YES

B/ NO
During insertion, active medical substance is released from the rod to support cervical ripening/dilation.

A/ YES

B/ NO. DILAPAN-S doesn’t contain any active substances, which could release during its use.
Quiz / part 1
Question 8

Which of following DILAPAN-S indications is not correct:

A/ cervical preparation prior to surgical hysteroscopy
B/ preinduction of labour
C/ cervical preparation prior to fetal demise
D/ cervical preparation prior to hysterectomy
Which of following DILAPAN-S indications is not correct:

A/ cervical preparation prior to surgical hysteroscopy
B/ preinduction of labour
C/ cervical preparation prior to fetal demise
D/ cervical preparation prior to hysterectomy (hysterectomy is a surgical removal of the uterus). HysteroSCOPY is the right term.
DILAPAN-S

Market and competitors overview / DILAPAN-S key benefits /
DILAPAN-S

IOL
Definitions:
- Labor induction: intervention (either through medical or other methods) designed to artificially initiate uterine contractions leading to vaginal birth of the baby.
- Cervical ripening (synonyms: labor pre-induction, labor induction with unfavourable cervix): set of methods that lead to cervical maturation in terms of dilation, shortening and swelling.

Labor is usually induced
- For medical reasons (mother / baby at risk)
- Elective induction: it is not done for medical reasons (mother’s own decision - fear of risks, convenience,..)

Approx. 20-30% of labors start artificially and need to be induced.

BUT
No each labor induction is connected with unfavourable cervix / up to 50% of induced labors need cervical ripening (= 10% of total labors)
Cervical ripening prior to labor induction / IOL

2 steps procedure

<table>
<thead>
<tr>
<th>Cervix status</th>
<th>1st step</th>
<th>2nd step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ripe / favorable</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Unripe / unfavorable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If the cervix is favorable, labor can be induced directly. BUT if the cervix is unfavorable, 1st step is to prepare cervical canal.

“Successful labour induction is clearly related to the state of the cervix. Women with an unfavorable cervix, who have not experienced cervical ripening phase before labor, present the greatest challenge with regard to labor induction.”
Cervical ripening prior to labor induction / IOL
Bishop / cervix score* (BS)

The status of the cervix can be determined by the Bishop scoring system

<table>
<thead>
<tr>
<th>Score</th>
<th>Dilation (cm)</th>
<th>Position of Cervix</th>
<th>Effacement (%)</th>
<th>Station*</th>
<th>Cervical Consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Closed</td>
<td>Posterior</td>
<td>0–30</td>
<td>-3</td>
<td>Firm</td>
</tr>
<tr>
<td>1</td>
<td>1–2</td>
<td>Midposition</td>
<td>40–50</td>
<td>-2</td>
<td>Medium</td>
</tr>
<tr>
<td>2</td>
<td>3–4</td>
<td>Anterior</td>
<td>60–70</td>
<td>-1, 0</td>
<td>Soft</td>
</tr>
<tr>
<td>3</td>
<td>5–6</td>
<td>—</td>
<td>80</td>
<td>+1, +2</td>
<td>—</td>
</tr>
</tbody>
</table>

*Station reflects a −3 to +3 scale.

Max 13 points can be reached.

„An unfavourable cervix is generally defined as a Bishop score of 6 or less. If the total score is **more then 8**, the probability of vaginal delivery after labor induction is similar to that after spontaneous labor.“

!!! more versions of Bishop score exist such as **10 points scale** (then score 5 represents limit to evaluate the cervix as un/favourable.!!!
Cervical ripening prior to labor induction / IOL

Market needs / methods

Customer needs:
• To reach vaginal delivery – “vaginal delivery rate“
• To ensure cervical ripening enabling labor induction – „Bishop score“
• To minimize / avoid safety risks for mother and newborn
• Cost-effectiveness, time,… „vaginal delivery within 24/36 hrs“

Methods:
• Pharmacological
• Mechanical

„Onset of regular uterine activity as a result of pre-induction is a negative and unwanted side effect. “

„The principal role of the agents used for cervical ripening is to soften an unripe cervix independent of uterine activity. “
Cervical ripening prior to labor induction / IOL

Methods and competitors

It is crucial to distinguish between methods being used for

<table>
<thead>
<tr>
<th>Cervical ripening</th>
<th>Labour induction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical</strong></td>
<td><strong>Mechanical</strong></td>
</tr>
<tr>
<td>DILAPAN-S</td>
<td>Amniotomy</td>
</tr>
<tr>
<td>(Laminaria)</td>
<td>(rupture of membranes)</td>
</tr>
<tr>
<td>Ripenning double balloon</td>
<td><a href="http://www.youtube.com/watch?v=tcjW1zamW">http://www.youtube.com/watch?v=tcjW1zamW</a></td>
</tr>
<tr>
<td>Foley catheter</td>
<td></td>
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<tr>
<td>Membrane sweeping</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacological</strong> **</td>
<td><strong>Pharmacological</strong> **</td>
</tr>
<tr>
<td>Dinoprostone</td>
<td>Oxytocin</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Misoprostol</td>
</tr>
</tbody>
</table>

It happens that the use of cervical ripening agents switch to spontaneous labor and no further induction is needed

** the use of misoprostol or some formulations of dinoprostone (such as vaginal tablets) can cover both steps simultaneously

!!! Oxytocin is not direct competitor to DILAPAN-S !!!
Cervical ripening prior to labor induction / IOL
Competitors overview / mechanical methods

DILAPAN-S

• Clinical outcomes
  – Cervical ripening success rate: 94%
  – Vaginal delivery rate +/- 80%
  – OXY/PGE administration to induce labor is required in approx. 80%
  – No serious SEs
  – No uterine hyperstimulation or fetal distress during cervical ripening
  – Uterine contraction in 31% of patients (mild only)
  – No infection complications reported
  – Excellent rate of patients' satisfaction
    • 93.7% evaluated Dilapan-S insertion as fully acceptable
    • 89.5% stated they could relax during cervical ripening period
    • 79% stated they could sleep during cervical ripening period
## DILAPAN-S

### Key strenghts / weaknesses

<table>
<thead>
<tr>
<th>Key strengths</th>
<th>Key weaknesses</th>
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</thead>
<tbody>
<tr>
<td>- <strong>Good efficacy</strong> in terms of Bishop score increase</td>
<td>- No randomised clinical trials up today</td>
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<tr>
<td>- High predictability</td>
<td>- Depends on local rules can happen that the product can be inserted by doctors only (&quot;invasive method&quot;)</td>
</tr>
<tr>
<td>- <strong>Very good safety profile</strong> / no pharmacological side effects</td>
<td>- Insertion procedure is more time consuming then PGE</td>
</tr>
<tr>
<td>- Clinical data confirming its efficacy and safety even in women with previous C. section</td>
<td>- Can be more difficult to be used in cases with partially dilated cervix – more pieces have to be used</td>
</tr>
<tr>
<td>- One-time application</td>
<td>- Higher price then Foley / misoprostol</td>
</tr>
<tr>
<td>- Can be used even in cases with highly unripe cervix (low Bishop score)</td>
<td></td>
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<tr>
<td>- Insertion easier / faster then Foley / balloon catheters</td>
<td></td>
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<tr>
<td>- <strong>High patients satisfaction</strong></td>
<td></td>
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<tr>
<td>- CTG monitoring is not requested / outpatients use.</td>
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<tr>
<td>- No specific storage requirements</td>
<td></td>
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<tr>
<td>- Higher cost-effectiveness then COOK double balloon, Propess or (Prepidil)</td>
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</tr>
</tbody>
</table>
Cervical ripening prior to labor induction / IOL Competitors overview / mechanical methods

DILAPAN-S

- **Size of choice**
  - DILAPAN-S 4x55mm should be the size of choice

- **Number of pieces**
  - 4-5 pieces are recommended, but generally as many Dilapan-S can be used as can be comfortably inserted (4-6) in situ
  - 2 pieces are sufficient to increase Bishop score enabling labor induction
  - The more pieces, the higher Bishop score (or shorten of cervical ripening period)
Cervical ripening prior to labor induction / IOL
Competitors overview / mechanical methods

Laminaria

- Similar mode of action as DILAPAN-S
- 100% natural – made of a sea-grown plant
- Rode size ranges from 2 to 10mm diameters and 60-85 mm in length
- Produced by several companies worldwide
  - The US / MedGyn, Norscan
  - Japan / NIPPON,…
- Very popular in Japan / widely used in the US

- Except JAPAN they is no feedback from the markets that Laminaria would be used in OBSTETRICS!! When on the market, it is used mainly in termination of pregnancy.

!! Laminaria doesn´t represent significant competitor in this indication !!

- VIDEO

See further information incl. Pros & Cons in Section Termination of pregnancy.
Cervical ripening prior to labor induction / IOL
Competitors overview / mechanical methods

Cervical ripening balloon / Foley catheter

- Single / double silicone balloon, which is gradually inflated with saline after insertion into the cervix and left for 12-24(48) hours

- In terms of inflation, more recommendations can be found based on official IFU / clinical experience (30 – 100ml / balloon)

- **Foley catheter**
  - Primarily developed as a urinary catheter
  - The product doesn’t have official IFU, so recommendations for its use come from clinical experience
  - Clinical studies have described its use for 12-24 or 48 hrs
  - If spontaneously detached, it can be replaced by new one to reach higher cervical ripening
  - Low price, approx. 3 USD
Cervical ripening prior to labor induction / IOL
Competitors overview / mechanical methods

Cervical ripening balloon / Foley catheter

- **Atad ripener device (double balloon device) / USA**
  - Coming from 90’s last century
  - FDA approved, but only a few clinical studies available
  - No info about its availability nowadays

- **COOK cervical ripening balloon / COOK Medical, USA**
  - Specially developed for cervical ripening
  - Maximum balloon inflation: 80 ml
  - Its use is limited up to 12 hours
  - A lot of contraindications and warnings in IFU
    - Patients planning to undergo exogenous prostaglandins administration
    - Rupture of membranes
    - Using in women with C. section in medical history
  - Usually high market price (50-80 USD)
Cervical ripening prior to labor induction / IOL

Competitors overview / mechanical methods

Cervical ripening balloon / Foley catheter

**Clinical outcomes**
- Vaginal delivery rate up to 80%
- Vaginal delivery within 24 hrs approx. 68%
- OXY / PGE administration to induce labor is required in approx. 85%
- Usualy no serious SEs / uterine hyperstimulations during cervical ripening

**Key strenghts / weaknesses**

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<tr>
<td>- Good efficacy in terms of Bishop score increase</td>
<td>- Insertion procedure is quite time consuming</td>
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<tr>
<td>- Very good safety profile / no pharmacological side effects</td>
<td>- Depends on local rules can happen that the product can be inserted by doctors only („invasive method“)</td>
</tr>
<tr>
<td>- Usualy one-time application</td>
<td>- Potential troubles with insertion to highly unripe cervix (soft silicone catheter)</td>
</tr>
<tr>
<td>- Can be used even in cases with partially dilated cervix (Bishop score close to 6)</td>
<td>- Initial inflation in short time can be painful for patient</td>
</tr>
<tr>
<td>- Foley catheter – low price</td>
<td>- Inconvenient for patients - the external end of the device is usualy taped on woman’s thigh / potential limitation in movement, showering,…</td>
</tr>
<tr>
<td></td>
<td>- COOK: high price</td>
</tr>
<tr>
<td></td>
<td>- COOK: maximum time of insertion is 12 hrs</td>
</tr>
<tr>
<td></td>
<td>- COOK: long list of contraindications and warnings</td>
</tr>
</tbody>
</table>
Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods
dinoprostone

- PGE$_2$

- Mode of action:
  - Prostaglandins cause collagen degradation, which softens the cervix and induce smooth muscle contractions, which results in uterine contractions

- Indication:
  - Cervical ripening in a patients at or near term

- A lot of products / different formulations / producers
  - Vaginal pessary: Propess / Cervidil
  - Intracervical gel: Prepidil, Cerviprime,…
  - Vaginal tablets: Prostin,…
Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods
dinoprostone

• **Clinically significant contraindication**
  - Previous Caesarean section

• **Warnings / Precautions**
  – Cardiovascular, liver, kidney disease, asthma, glaucoma,…
  – PROM (premature rupture of membranes)
  – Women aged 30 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of postpartum disseminated intravascular coagulation.
  – During use, uterine activity and fetal status should be carefully monitored to detect possible evidence of undesired responses, e.g., hypertonus, sustained uterine contractility, or fetal distress = **HOSPITAL USE ONLY**
  – I.v. oxytocin is recommended to be administered (if necessary) no earlier then 6 hours after dinoprostone administration

• **Storage condition**
  - Cold chain – freezer or refrigerator
Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods
dinoprostone

• **Vaginal pessary: Propess / Cervidil (Ferring Pharmaceutical)**
  – Brand Propess is used in Europe, Cervidil in the US and Canada
  – 10 mg dinoprostone vaginal delivery system
  – Continuous releasing of approx. 0.3 mg of dinoprostone / hour over 24 hours
  – Can be left in place for a maximum of 24 hours
  – Sufficient tape is left outside of vagina
  – One-time application - IFU, but clinicians claim 20-40% of patients need 2nd set application
  – Following administration patient should remain lying down
    for at least 20-30 minutes
  – Market price – EU usually 30 – 50 € / the US 200 USD
  – Storage conditions: in freezer
Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods
dinoprostone

- Intracervical gel: Prepidil (Pfizer), Cerviprime (Astra Zeneca),…
  - 3 g of intracervical gel containing 0.5 mg of dinoprostone
  - Administration can be repeated after 6 hours up to a maximum daily cumulative dosage 1.5 mg = multiple application. The need for additional dosing must be determined by physician. Based on literature search repeat application can be expected in approx. 50% of patients.
  - Following administration of the gel, patient should remain lying down for at least 15-30 minutes
  - Gel needs to be stored under continuous refrigeration (36° to 46°F; 2° to 8°C)
  - Price varies significantly based on territory
Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods
dinoprostone

- Vaginal tablets: Prostin (Pfizer),…
  - 1 vaginal tablet contains 3 mg of dinoprostone
  - IFU recommends to place 1 tablet of 3mg dinoprostone to posterior fornix of vagina. Another one tabler can be applied 6-8 later, maximum daily dosage is 6 mg
  - In daily clinical practice is routinely used lower dosage then 3mg, such as 1,5 mg or lower (tablet is cutted) to mimimise side effects risk. Then the administration is more frequently repeated.
  - Storage condition: in refrigerator
  - Low price
Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods
dinoprostone

**Clinical outcomes**

- Vaginal delivery rate approx. 75%
- Rate of vaginal delivery within 24 hours 51%
- Propess / Cervidil evaluated as more effective than intracervical gel*
- OXY administration to induce labor is expected in approx. 50%
  (big differences in clinical studies)
- Systemic side effects 24.7%
- Uterine contractions are common during cervical ripening period—50% or more
- Uterine hyperstimulation and fetal distress approx. 3 - 5%

Wing DA et al., Misoprostol Vaginal Insert and Time to Vaginal Delivery A Randomized Controlled Trial, Obstet Gynecol; Vol. 122, No. 2, Part 1, August 2013*
### Key strengths

- Good efficacy in terms of Bishop score increase
- Easy application (based on physicians perception)
- Can be applied by nurses
- Can be used even in cases with partially dilated cervix (Bishop score close to 6)
- Price can be very low depending on the formulation

### Key weaknesses

- Failure rate of Propess is 20-40%
- Risk of hyperstimulation and fetal distress
- Contraindicated in previous C. section
- HOSPITAL USE ONLY / CTG monitoring recommended
- Lower predictability
- Repeated application
- Propess / Cervidil – not easy to place based on midwifes feedback, risk of falling out
- Propess / Cervidil – high price
- A lot of Warnings and Precautions
- Risk of systemic side effects
- Inconvenient for patients - uterine contractions during ripening period are exhausting for patients (can’t relax, sleep)
- Cool chain storage condition - in freezer / refrigerator
Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods

misoprostol

• PGE₁
• Mode of action:
  – Similar to dinoprostone BUT much more stronger, so its use is associated with higher risk of uterine hyperstimulation / rupture
• Use in OBS / GYNE
  – Original indication: prevention of NSAID induced gastric ulcers
  – In many countries misoprostol is used in OBS / GYNE indications out of official label, BUT
  – WHO, national guidelines usually recommend misoprostol for cervical preparation / ripening
  – Research focused on identifying „ideal dosage“, which will combine efficacy and safety

• A lot of products / formulations / producers
  – Oral, sublingual / buccal, vaginal administration
• Misodel (Ferring Pharmaceutical)
  – 200 mcg miso controlled release vaginal delivery system
  – Approved in 2014 in EU for cervical ripening from 36 weeks of gestation
• Cytotec (Pfizer)
  – 100 of 200 mcg oral tablets
  – Officially contraindicated for pregnant women
Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods

misoprostol

• Clinical outcomes
  – Dossage current recommendation
    • 25 - 50 mcg per oral or vaginally every 4 hours
    • Administration is usually repeated 2-4 times
  – Vaginal delivery rate approx. 75%
  – Rate of vaginal delivery within 24 hours 65%
  – Uterine hyperstimulation and fetal distress vary from 10 to 30%
  – Risk of meconium staining (meconium aspiration syndrome)
  – Uterine contractions are common during cervical ripening period
  – Systemic side effects are quite common – 25%
  – It is still unclear, which administration is better
    • Vaginal administration seems to be superior in terms of decreasing systemic side effects, but sometimes evaluated as promoting more uterine hyperstimulations
    • Oral administration is preferred by patients and in some studies evaluated as more effective and safe...
  – OXY administration to induce labor is expected in up to 35 % of patients

Cervical ripening prior to labor induction / IOL
Competitors overview / pharmacological methods
misoprostol

- **Key strengths / weaknesses**

<table>
<thead>
<tr>
<th>Key strengths</th>
<th>Key weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High efficacy</td>
<td>- High risk of hyperstimulation, fetal distress and meconium stained</td>
</tr>
<tr>
<td>- Easy administration (incl. theor. patient’s self-administration at home)</td>
<td>- Lower predictability</td>
</tr>
<tr>
<td>- A lot of „spontaneous“ publications supporting the product visibility</td>
<td>- Usually not used in cases with previous C. section</td>
</tr>
<tr>
<td>- Very cheap</td>
<td>- Usually HOSPITAL USE ONLY / CTG monitoring recommended</td>
</tr>
<tr>
<td>- Recommended by WHO and many national guidelines</td>
<td>- Repeated application requiring doctor’s time for decision</td>
</tr>
<tr>
<td>- No special requirements for storage</td>
<td>- Risk of systemic side effects</td>
</tr>
<tr>
<td>- No IFU / no official limitations</td>
<td>- Inconvenient for patients - uterine contractions during ripening period are exhausting for patients (can’t relax, sleep)</td>
</tr>
<tr>
<td></td>
<td>- Risk of uterine rupture</td>
</tr>
</tbody>
</table>
Cervical ripening prior to labor induction / IOL Competitors overview

Summary

<table>
<thead>
<tr>
<th>DILAPAN-S / DILASOFT</th>
<th>PHARMACOLOGICAL METHODS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Similar efficacy as pharmacological methods</td>
<td></td>
</tr>
<tr>
<td>• Minimal safety concerns even in high-risk patients</td>
<td></td>
</tr>
<tr>
<td>• Suitable for VBAC</td>
<td></td>
</tr>
<tr>
<td>• Low, if any, uterine contractions during cervical ripening phase</td>
<td></td>
</tr>
<tr>
<td>• No need of continuous CTG monitoring</td>
<td></td>
</tr>
<tr>
<td>• Patient comfort and tolerability</td>
<td></td>
</tr>
<tr>
<td>• More frequent need of oxytocin augmentation</td>
<td></td>
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<td>• One-time application = time savings</td>
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<tr>
<td>• Perceived as effective</td>
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<tr>
<td>• Concerns of uterine hyperstimulation and fetal heart rate changes (not acceptable in high-risk patients)</td>
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<tr>
<td>• Uterine activity not desired during cervical ripening phase</td>
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<tr>
<td>• Need of continuous CTG monitoring during preinduction</td>
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<tr>
<td>• Patient’s discomfort and pain</td>
<td></td>
</tr>
<tr>
<td>• Less frequent need of oxytocin augmentation</td>
<td></td>
</tr>
<tr>
<td>• Usually required repeated application</td>
<td></td>
</tr>
</tbody>
</table>
DILAPAN-S

Video - IOL
Cervical preparation prior to termination of pregnancy / TOP

Market overview

Definitions:

• **Termination of pregnancy / induced abortion**: removal or expulsion of fetus or embryo from the uterus prior to viability
  
  – **1st trimester**: up to 12 weeks / medical reasons worldwide, women's decision in some regions / 90% of all abortions
  
  – **2nd trimester**: 12-24 weeks / Medical reasons only / 10% of total abortions

• **Fetal demise**: Fetal demise is a medical term used to refer to the situation when the fetus has died. Normally diagnosed via ultrasound when no heart beat is found, it can also be diagnosed through laboratory studies.
Cervical preparation prior to termination of pregnancy / TOP

Market overview

Definitions:

- **Medical abortion:**
  - The use of pharmacological products (misoprostol, mifepristone, alone or in combinations) to terminate the pregnancy
  - Cervical preparation and fetus evacuation is proceed in one step

- **Surgical abortion:**
  - The use of surgical methods to evacuate uterine cavity
  - **Vacuum aspiration (suction apriation):** specially designed syringe is used to apply suction
  - **D&C procedure (dilation and curretage):** dilation of the cervix and surgical removal of part of the lining of the uterus. It is a therapeutic gyne procedure as well method of first trimester abortion
  - **D&E procedure (dilation and evacuation):** dilation of the cervix and evacuation of the uterine cavity. Method of second trimester abortion.
<table>
<thead>
<tr>
<th>Method</th>
<th>1st trimester</th>
<th>2nd trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical abortion</strong></td>
<td><strong>Mifepristone + misoprostol</strong></td>
<td><strong>Misoprostol + mifepristone</strong></td>
</tr>
<tr>
<td></td>
<td>Misoprostol alone can be use if mifepristone in not available</td>
<td>Alternative regimens such as misoprostol alone should only be used when mifepristone is not available</td>
</tr>
<tr>
<td></td>
<td>Dedicated cervical preparation is not requested</td>
<td>Proof of concept that DILAPAN-S use in combination is beneficial</td>
</tr>
<tr>
<td><strong>Surgical abortion</strong></td>
<td><strong>Vacuum aspiration</strong> <em>(prior to 7 weeks of gestation)</em></td>
<td><strong>D&amp;E procedure</strong></td>
</tr>
<tr>
<td></td>
<td>Cervical dilation is usually not needed. If YES, rigid dilators are used.</td>
<td>Cervical preparation is essential</td>
</tr>
<tr>
<td></td>
<td><strong>D&amp;C / D&amp;E procedure</strong> <em>(late 1st trimester)</em></td>
<td>DILAPAN-S</td>
</tr>
<tr>
<td></td>
<td>Cervical preparation is requested</td>
<td>Laminaria</td>
</tr>
<tr>
<td></td>
<td>Osmotic dilators</td>
<td>misoprostol</td>
</tr>
<tr>
<td></td>
<td>misoprostol</td>
<td>(rigid dilators)</td>
</tr>
</tbody>
</table>
# Cervical ripening prior to termination of pregnancy / TOP

## Methods

<table>
<thead>
<tr>
<th></th>
<th>1st trimester</th>
<th>2nd trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical abortion</strong></td>
<td><strong>Mifepristone + misoprostol</strong>&lt;br&gt;Misoprostol alone can be used if mifepristone is not available</td>
<td><strong>Misoprostol + mifepristone</strong>&lt;br&gt;Alternative regimens such as misoprostol alone should only be used when mifepristone is not available</td>
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</tr>
<tr>
<td></td>
<td><strong>D&amp;C / D&amp;E procedure</strong>&lt;br&gt;(late 1st trimester)&lt;br&gt;Cervical preparation is requested&lt;br&gt;Osmotic dilators&lt;br&gt;misoprostol&lt;br&gt;(rigid dilators)</td>
<td><strong>DILAPAN-S</strong>&lt;br&gt;Laminaria misoprostol</td>
</tr>
</tbody>
</table>
Cervical preparation prior to termination of pregnancy / TOP

Market needs in surgical abortion

Customer needs:
- Safe procedure
- To minimize risk of complications (early / late)
- To shorten time needed for procedure – same day procedure

Competitors:
- Misoprostol
- Laminaria
- (rigid dilators)
Cervical preparation prior to termination of pregnancy / TOP Competitors overview

DILAPAN-S

• Clinical outcomes

Vs misoprostol
  — Late 1st and early 2nd trimester:
    • 1 piece of DILAPAN-S is more effective, when used 3-4 hours before procedure
  — 2nd trimester:
    • DILAPAN-S offers higher efficacy and better predictability enabling to avoid challenging situations in same day D&E procedure
    • Patients and physicians can benefit from combination of DILAPAN-S and misoprostole before D&E procedure in late second trimester

Vs Laminaria
  — DILAPAN-S is suitable for same-day procedure
  — Is faster, able to reach higher dilation
  — Approximately half the number of Dilapan-S is needed
  — SFP guidelines evaluated DILAPAN-S as the best product in its class of osmotic cervical dilators
Cervical preparation prior to termination of pregnancy / TOP Competitors overview

DILAPAN-S

- **Key strengths / weaknesses**

<table>
<thead>
<tr>
<th>Key strengths</th>
<th>Key weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Excelent efficacy</td>
<td>- Insertion requires time and patient’s presence at abortion clinic before procedure, when compared with misoprostol</td>
</tr>
<tr>
<td>- High predictability and consistency of action</td>
<td>- „Dumbbeling“ issue</td>
</tr>
<tr>
<td>- Very good safety profile / no pharmacological side effects</td>
<td>- More expensive then misoprostol</td>
</tr>
<tr>
<td>- No challenging situations during cervical preparation when compared with misoprostol</td>
<td></td>
</tr>
<tr>
<td>- Suitable for same-day procedure</td>
<td></td>
</tr>
<tr>
<td>- Outpatients use</td>
<td></td>
</tr>
</tbody>
</table>

- **Size of choice / number of pieces**

- One piece can used for cervical preparation prior to termination of pregnancy or fetal demise up to 16 weeks of gestation.
- DILAPAN-S 3 x 55 mm or 4 x 55 mm should be the size of choice.
- Usualy 2-5 pieces are used for cervical preparation prior to termination of pregnancy in the 2\textsuperscript{nd} trimester.
- DILAPAN-S 4 x 65 mm should be the size of choice.
Cervical preparation prior to termination of pregnancy / TOP
Competitors overview

misoprostol

**Clinical outcomes**

- 200 – 800 mcg usually used for cervical preparation / 400 mcg is used most commonly
- Oral, buccal, sublingual or vaginal administration
- Same-day administration up to 18 weeks of gestation
- Systemic side effects: cramping, nausea, vomiting, diarrhea, fever
- Highly effective in cervical preparation, but less than DILAPAN-S in late 1st and 2nd trimester

*Boulvain: Cochrane Database Syst Review, 2008*
Cervical preparation prior to termination of pregnancy / TOP Competitors overview

misoprostol

- **Key strengths / weaknesses**

<table>
<thead>
<tr>
<th>Key strengths</th>
<th>Key weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High efficacy</td>
<td>- Less preoperative dilation then DILAPAN-S</td>
</tr>
<tr>
<td>- Easy administration (incl. theor. patient’s self-administration at home)</td>
<td>- Lower predictability</td>
</tr>
<tr>
<td>- A lot of „spontaneous“ publications supporting the product visibility</td>
<td>- Risk of systemic side effects</td>
</tr>
<tr>
<td>- Very cheap</td>
<td></td>
</tr>
<tr>
<td>- Recommended by WHO and many national guidelines</td>
<td></td>
</tr>
<tr>
<td>- No IFU / no official limitations</td>
<td></td>
</tr>
</tbody>
</table>
Cervical preparation prior to termination of pregnancy / TOP Competitors overview

Laminaria

- **Key strengths / weaknesses**

<table>
<thead>
<tr>
<th>Key strengths</th>
<th>Key weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Long-term clinical experience and doctor’s habit</td>
<td>- Limited efficacy / slow action</td>
</tr>
<tr>
<td>- Lower price/ piece when compared with DILAPAN-S</td>
<td>- Unpredictability and inconsistency of action due to natural product</td>
</tr>
<tr>
<td>- No pharmacological side effects</td>
<td>- Not suitable for same-day procedure</td>
</tr>
<tr>
<td></td>
<td>- Risk of infections</td>
</tr>
<tr>
<td></td>
<td>- Risk of allergic reaction</td>
</tr>
</tbody>
</table>
Competitors overview

Lamicel

Nowadays probably available in Japan only

- dehydrated polyvinyl alcohol sponge embedded with 450 mg of magnesium sulfate
- Rods are 67 mm long and 3 or 5 mm in diameter
- Even when maximally dilated the sponge is compressible and does not exert radial force within the cervix.
- Lamicel may work by inciting prostaglandin synthesis or by stimulating collagenolytic activity within the cervical stroma, but the exact mechanism of action is unclear.
- Limited clinical evidence
- Owned and produced by Medtronic Xomed, Inc., Cabot Medical Corporation

<table>
<thead>
<tr>
<th>Key strengths</th>
<th>Key limitation factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pharma SEs</td>
<td>Unclear mode of action</td>
</tr>
<tr>
<td></td>
<td>Lower dilation  in comparison with other osmotic dilators</td>
</tr>
<tr>
<td></td>
<td>Non-effective in cervical preparation in late second trimester</td>
</tr>
<tr>
<td></td>
<td>Limited clinical evidence</td>
</tr>
</tbody>
</table>
Competitors overview

Metal / plastic dilators

• Different diameter of metal rods
• The thin rod is inserted to the cervix and briefly left in place, taken out, and replaced by a slightly larger rod; this process is repeated until the cervix is wide enough
• It takes about 10 minutes
• No pharmaceuticals involved
• Many producers, no dominant player

<table>
<thead>
<tr>
<th>Key strengths</th>
<th>Key limitation factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low price</td>
<td>Risk of cervical injury / risk of damaging the function of the cervix for the future pregnancy</td>
</tr>
<tr>
<td>Simple use for doctors</td>
<td></td>
</tr>
<tr>
<td>The procedure is fast</td>
<td></td>
</tr>
</tbody>
</table>
DILAPAN-S

Other indications
Cervical preparation prior to hysteroscopy

Definition:
• Inspection of the uterine cavity by endoscopy, accession through the cervix. It allows for the diagnosis of intrauterine pathology and serves as a method for surgical intervention (operative hysteroscopy).

Competitors:
• Rigid dilators
• Laminaria
• misoprostol

Size of choice, number of pieces:
• One piece
• DILAPAN-S 3 x 55 mm should be the size of choice.

Key benefits:
• Similar to them for termination of pregnancy

Expected time in situ:
• up to 4 hrs based on required dilation
IUD extraction / insertion

Definitions:

- **IUD - Intrauterine Device**: it is a form of birth control in which a small 'T-shaped' device, containing either copper or progesterone, is inserted into the uterus. IUDs are a form of long-acting reversible contraception, which is the most effective type of reversible birth control.

- **Cervical preparation**: dilation of the cervix in cases where IUD insertion or removal is difficult / impossible due to the state of the cervix.

It is estimated, that up to 10% of IUD insertion and up to 25% of IUD removals can benefit from cervical preparation.

Positive trend – No. of IUD users is rapidly increasing.

New market, no clinical data directly with DILAPAN-S. Efficacy and safety can be anticipated according further indications.
IUD extraction / insertion
Market needs / competitors / benefits

Customer needs:
• Have to be verified by market survey
• Assumed: gentle cervical dilation ensuring smooth IUD insertion / removal

Competition:
• Ridig dilators
• misoprostol

DILAPAN-S potential benefits:
• Fast, effective and safe cervical preparation
  — Gradual non-traumatic cervical preparation
  — No pharmacological side effects
  — The greatest cervical dilation in the shortest timeframe of any osmotic dilator
• Very high patient acceptability
• Easier one-step procedure vs combinations of pharma methods + rigid dilators

Size of choice, number of pieces:
• One piece
• DILAPAN-S 3 x 55 mm should be the size of choice.
IVF / Embryo transfer

Definitions:

- **IVF - In vitro fertilization:** is a process by which an egg is fertilized by sperm outside the body. IVF is a key treatment for infertility when other methods of assisted reproductive technology have failed.
- **Embryo transfer:** embryo implantation into the uterus.
- **Cervical preparation:** dilation of the cervix in cases where embryo transfer is impossible due to the state of the cervix

It is assumed that at least 10% of embryo transfer procedures can benefit from cervical preparation (these are called difficult embryo transfer). Appropriate cervical preparation can significantly increase implantation rate.

Positive trend - number of IVF procedures is increasing.
Market needs / competitors / benefits

Customer needs:
• To transfer embryo through the cervix to the uterine cavity as easily as possible. Difficulties during the embryo transfer usually significantly reduce implantation rate.

Methods being used for difficult embryo transfer:
• Special cannula, but with clinical limitations / does not meet need

Competitors:
• …?

DILAPAN-S potential benefits:
• Fast, effective and safe cervical preparation
  – Gradual non-traumatic cervical preparation
• Very high patient acceptability

Size of choice, number of pieces:
• One piece
• DILAPAN-S 3 x 55 mm should be the size of choice
DILAPAN-S

Market potential
Market potential

Market potential can be easily calculated

<table>
<thead>
<tr>
<th>Indication</th>
<th>No of cases</th>
<th>No of pieces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinduction of labour (5% of total)</td>
<td>No of labours / Year * 0.05</td>
<td>2-3 pieces / case</td>
</tr>
<tr>
<td>Termination of pregnancy (late) 1st trimester</td>
<td>Source: national statistics / KOL’s</td>
<td>1 piece / case</td>
</tr>
<tr>
<td>Termination of pregnancy 2nd trimester</td>
<td>3 pieces / case</td>
<td></td>
</tr>
<tr>
<td>IUD extraction / insertion</td>
<td>10 – 25% of cases</td>
<td>1 piece / case</td>
</tr>
<tr>
<td>IVF</td>
<td>10% of embryo transfer’s cycles</td>
<td>1 piece / case</td>
</tr>
</tbody>
</table>
DILAPAN-S

Quiz

Part 2
What are the aims of cervical ripening and labour induction?
What are the aims of cervical ripening and labor induction?

Cervical ripening: to ripen the cervix in terms of its softening, shortening, opening,..

Labor induction: to provoke uterine contraction to reach vaginal delivery.
Which of the following products doesn’t belong to cervical ripening agents:

A/ misoprostol
B/ Foley catheter
C/ oxytocin
D/ Dilapan-S
Which of the following products doesn’t belong to cervical ripening agents:

A/ misoprostol

B/ Foley catheter

C/ oxytocin

D/ Dilapan-S
Onset of regular uterine activity during cervical ripening phase is:

A/ welcome, it helps to mature the cervix and accelerate the labor

B/ unwanted, only causes the pain to woman and increases the risk of fetal distress

C/ unimportant, it doesn’t have any, as positive as negative, impact of this phase of labor
Onset of regular uterine activity during cervical ripening phase is:

A/ welcome, it helps to mature the cervix and accelerate the labor

B/ unwanted, only causes the pain to woman and increases the risk of fetal distress

C/ unimportant, it doesn’t have any, as positive as negative, impact of this phase of labor
How many pieces of Dilapan-S is recommended to use for cervical dilation prior to termination of pregnancy in 14th week of gestation?

A/ 1 piece

B/ 2 pieces

C/ 3 pieces
How many pieces of Dilapan-S is recommended to use for cervical dilation prior to termination of pregnancy in 12th week of gestation?

A/ 1 piece

B/ 2 pieces

C/ 3 pieces
Bishop score helps to health care professionals:

A/ to quantify number of uterine contractions

B/ to identify maturity of the cervix

C/ to assume total length of the labor
Bishop score helps to health care professionals:

A/ to quantify number of uterine contractions

B/ to identify maturity of the cervix

C/ to assume total length of the labor
Quiz / part 2

Question 6

Dilapan-S doesn’t provoke uterine contraction.

A/ True

B/ False
Dilapan-S doesn’t provoke uterine contraction.

A/ True

B/ False. Uterine contraction can be recorded during Dilapan-S use, but usually in lower frequency and mild intensity when compared with prostaglandines.
Quiz / part 2

Question 7

How many pieces of Dilapan-S are generally recommended for cervical ripening?

A/ 1 piece

B/ 2-3 pieces

C/ 4 or more
How many pieces of Dilapan-S are generally recommended for cervical ripening?

A/ 1 piece

B/ 2-3 pieces

C/ 4 or more
Which of the following products requests special storage conditions and what?

A/ dinoprostone

B/ Foley catheter

C/ Dilapan-S

D/ misoprostol
Which of the following products requests special storage conditions and what?

A/ dinoprostone. Cool chain (storage at 2-8°C)

B/ Foley catheter

C/ Dilapan-S

D/ misoprostol
DILAPAN-S

Key clinical evidence
Key clinical evidence

Jozwiak et al.: Mechanical methods for induction of labour (Review)
The Cochrane Collaboration, 2012

- The review includes 71 randomised controlled trials
- Mechanical methods versus vaginal PGE2, intracervical PGE2 and misoprostol:
  - No significant difference in the proportion of women not achieving vaginal delivery within 24 hours.
  - Mechanical methods reduced the risk of hyperstimulation with fetal heart rate changes when compared with vaginal PGE2 and misoprostol
  - Risk of caesarean section between mechanical methods and prostaglandins was comparable.
  - Serious neonatal and maternal morbidity were infrequently reported and did not differ between the groups.
  - Few studies addressed the issue of infection, which appeared not to be higher when using mechanical methods.
- Mechanical methods compared with induction with oxytocin:
  - Reduced the risk of caesarean section
  - Hyperstimulation with fetal heart rate changes was reported in one study and did not differ. There were no reported cases of severe maternal or neonatal morbidity.
Key clinical evidence / IOL

DILAPAN-S

• International observational clinical trial „e-registry“ on the use of DILAPAN-S for cervical ripening prior to labor induction
  – 11 study sites from 7 countries
  – 444 patients enrolled

• Prospective clinical trial comparing DILAPAN-S with PGE2 and Estradiol gel
  – 247 patients randomised, 82 treated by DILAPAN-S

• Prospective observational multicentre data collection on the use of DILAPAN-S in labor preinduction in women with / without Caesarean section in medical history
  – 6 study sites collecting data from 96 patients

• Prospective observational study evaluating DILAPAN-S efficacy and safety
  – 92 patients enrolled

• Retrospective study evaluating efficacy and safety of DILAPAN-S in labor preinduction
  – 68 patients enrolled, incl. post CS
Key clinical evidence / IOL

DILAPAN-S

- International observational clinical trial „e-registry“ on the use of DILAPAN-S for cervical ripening prior to labor induction

  - Data to be presented tomorrow

- Prospective clinical trial comparing DILAPAN-S with PGE2 and Estradiol gel
- Prospective observational multicentre data collection on the use of DILAPAN-S in labor preinduction in women with / without Caesarean section in medical history
- Prospective observational study evaluating DILAPAN-S efficacy and safety
- Retrospective study evaluating efficacy and safety of DILAPAN-S in labor preinduction

- See Dilapan-S webpage / Section for distributors / Literature
**Key clinical evidence / IOL**

**Cervical ripening / conclusion**

- Dilapan-S offers similar or higher efficacy as pharmacological agents.

- From safety point of view, Dilapan-S offers lower risk of uterine hyperactivity and fetal distress.

- No higher risk of maternal / neonatal morbidity has been recorded with Dilapan-S.

- Data confirm efficacy and safety of the use of Dilapan-S even in high risk groups of patients (previous CS, hypertension, DM, higher age, PROM).
Key clinical evidence / TOP

Cervical preparation prior to abortions

• International, multicentre observational clinical trial "e-registry"/ Efficacy and safety of Dilapan-S prior to Medical or Surgical abortion


• Bartz, D. et al.: Buccal misoprostol compared with synthetic osmotic cervical dilator before surgical abortion. Obstetrics & Gynecology, July 2013


• Lyus et al: Outcomes with same-day cervical preparation with Dilapan-S osmotic dilators and vaginal misoprostol before dilatation and evacuation at 18 to 21+6 weeks’ gestation, Contraception, Vol 87, Issue 1, p 71-75, Jan 2013

Key clinical evidence / TOP

Cervical preparation prior to abortions

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• See Dilapan-S webpage / Section for distributors / Literature
Key clinical evidence

Cervical preparation prior to abortions

Newmann S et al.: Same-Day Synthetic Osmotic Dilators Compared With Overnight Laminaria Before Abortion at 14–18 Weeks of Gestation

Internat Obstet Gynecol 2014;123:271–8

- 36 women were randomized to same-day synthetic osmotic dilators and 36 to overnight Laminaria.
- Mean procedure duration was 5.9 minutes for overnight Laminaria group and 8.1 minutes for same-day Dilapan-S group, with a mean difference of 2.1 minutes.
- There was no difference in complications, all of which were minor, or in the median procedural difficulty score rated by physicians.
- Most patients in both groups would choose a same-day procedure, if necessary in the future.
- Same-day synthetic osmotic dilators Dilapan-S are not inferior to overnight Laminaria with respect to procedure duration. Same-day osmotic dilation is preferred by patients and may be a reasonable alternative to overnight Laminaria for cervical preparation before early second-trimester dilation and evacuation.
Key clinical evidence

Cervical preparation prior to abortions

Bartz et al: Buccal Misoprostol Compared With Synthetic Osmotic Cervical Dilator Before Surgical Abortion.
A Randomized Controlled Trial

Contraception, 2014

- When compared with buccal misoprostole, 1 piece of DILAPAN-S offers higher efficacy in cervical dilation, when used 3-4 hours before procedure in late first trimester and early second trimester pregnancy termination.
- Thank’s to its predictability and rapid onset of action in first hours after insertion, DILAPAN-S offers high quality of cervical preparation for 1day D&E procedure.
- DILAPAN-S is effective and safe in women with Caesarean Section in medical history.
Cervical preparation for second-trimester surgical abortion prior to 20 weeks' gestation

The following recommendations are based on good and consistent scientific evidence (Level A):

• Cervical preparation is recommended prior to second trimester D&E to decrease risk of cervical trauma.

• Osmotic dilators (laminaria and Dilapan-S™) are safe and effective for cervical preparation prior to D&E.

• Use of osmotic dilators does not increase infectious morbidity.

• When osmotic dilator placement and D&E are to be performed on the same day, Dilapan-S™ is preferred over laminaria tents to achieve adequate priming more quickly.

• Osmotic dilators achieve more preoperative dilation than mifepristone or misoprostol.

Fox M et al. Cervical preparation for second-trimester surgical abortion prior to 20 weeks' gestation SFP Guideline #2013-4; Contraception 89 (2014) :75–84
Key clinical evidence

Cervical preparation prior to abortions

Society for Family Planning Clinical Guidelines: Cervical preparation for second-trimester surgical abortion prior to 20 weeks' gestation

Contraception, 2014

• Medical regimens may be more unpredictable in terms of the dilation achieved, the time needed to achieve adequate preparation and the risk of spontaneous delivery before D&E; thus, they may not be feasible or appropriate in some clinical settings.

• Efficacy of Dilapan-S enables same day D&E procedure in late first and second trimester

• In comparison with misoprostol, Dilapan-S offers higher efficacy and better predictability helping to avoid challenging situations including pharmacological side effects.

Fox M et al. Cervical preparation for second-trimester surgical abortion prior to 20 weeks' gestation SFP Guideline #2013-4; Contraception 89 (2014) :75–84
Key clinical evidence
Cervical preparation prior to abortions

Lyus et al: Outcomes with same-day cervical preparation with Dilapan-S osmotic dilators and vaginal misoprostol before dilatation and evacuation at 18 to 21+6 weeks’ gestation
Contraception, Vol 87, Issue 1, p 71-75, Jan 2013

- The safety and efficacy of a same-day preparation protocol using a combination of Dilapan-S and misoprostol for gestations of 18–22 weeks
- Three Dilapan-S dilators were inserted. Mean cervical preparation time was 3 h and 40 min, mean procedure time was 10 min
- There were no cases of uterine perforation, hemorrhage or inability to complete the procedure.
- This study suggests that same-day cervical preparation with Dilapan-S and misoprostol is safe and feasible for second-trimester surgical abortion up to 22 weeks’ gestation.
Key clinical evidence

Cervical preparation prior to abortions

Chambers et al.: Comparison of Dilapan-S and laminaria for cervical priming before surgical pregnancy termination at 17–22 weeks’ gestation

International Journal fo Women’s Health, 2011

- Adequate cervical priming for dilatation and evacuation (D&E) on Day 2 was achieved in 98% of the Dilapan-S cohort and 56% of cohort A and 40% of the cohort B laminaria cohorts
- A mean D&E theater time of 19 minutes for laminaria cohort A was reduced by 10.1% in the Dilapan-S cohort C.
- The incidence of unscheduled overnight delivery outside the clinic was 0% for Dilapan-S and 1.3% for cohort A and 3.8% for cohort B laminaria cohorts
- Dilapan-S osmotic dilators are superior to laminaria in producing more cervical priming and dilatation in a shorter time. This enables 17–22 week D&E procedures to be carried out in fewer days and in shorter theater times. They also eliminate the risk of an unscheduled overnight delivery outside the clinic.
Key clinical evidence

Cervical preparation prior to abortions / conclusion

- In late 1\textsuperscript{st} and 2\textsuperscript{nd} trimester Dilapan-S offers excellent efficacy in cervical dilation and is evaluated as superior to misoprostol.

- Dilapan-S is suitable for 1 day D&E procedure.

- In late 1\textsuperscript{st} trimester abortions, 1 piece of Dilapan-S for 4 hours ensures adequate cervical preparation.

- Dilapan- is the best product in its class of osmotic cervical dilators.
Key clinical evidence

Cervical preparation prior to difficult embryo transfer

Serhal et al: Cervical dilatation with hygroscopic rods prior to ovarian stimulation facilitates embryo transfer

Human reproduction, 2003

• Embryo transfer is a critical factor affecting the success of IVF and the ease of embryo transfer has a direct impact on the success rate.

• 54 patients

• 1 rod of Dilapan-S 3x55mm was placed and left for 4 h prior to starting gonadotrophin stimulation as an outpatient procedure.

• Of the 54 patients who originally had difficult embryo transfer, 43 patients (79.5%) had subsequent easy embryo transfer.

• Thirty patients managed to conceive, giving a clinical pregnancy rate of 55%.

• Cervical dilatation using hygroscopic dilators facilitates difficult embryo transfer and helps to improve the pregnancy rate.
Key clinical evidence

Dilapan-S vs Laminaria – in vitro experiment

Tomas Drunecky et al.: Experimental comparison of properties of natural and synthetic osmotic dilators
Arch Gynecol Obstet DOI 10.1007/s00404-015-3623-3, Published online 2015

- The in vitro study compares natural and synthetic osmotic dilators in selected parameters influencing their clinical efficacy.
- Diameters of Laminaria and synthetic dilators (Dilapan-S and Dilasoft) were measured in dry state, during free swelling in isotonic solution and during swelling against a force. Three aspects were evaluated—diameter increase, speed of action and consistency of action.
- Synthetic dilators compared to Laminaria reached higher maximum diameters, acted faster, were more consistent and were able to expand against force three times more.
- The results support clinical observations that synthetic dilators are more suitable and preferable for same-day D&E procedure and that fewer synthetic dilators are needed to achieve the same effect.
Dilapan-S superiority over Laminaria

Comparision of diameter change with increased time of swelling among Laminaria 4 mm, Dilapan-S 4x65 mm (non-buffered isotonic saline solution, 37°C)

Drunecky et al: Experimental comparison of properties of natural and synthetic osmotic dilators. ARCHIVES OF GYNECOLOGY AND OBSTETRICS, Feb 2015
Dilapan-S superiority over Laminaria

Predictability and consistency of action in diameter increase.

4 mm rods. Free swelling in isotonic saline infusion, 37°C

Drunecky et al: Experimental comparison of properties of natural and synthetic osmotic dilators. ARCHIVES OF GYNECOLOGY AND OBSTETRICS, Feb 2015
Dilapan-S superiority over Laminaria

Expansion force

Swelling against force in isotonic saline solution

Drunecky et al: Experimental comparison of properties of natural and synthetic osmotic dilators. ARCHIVES OF GYNECOLOGY AND OBSTETRICS, Feb 2015
DILAPAN-S

Marketing and Communication Strategy
Dilapan-S branding and communication strategy

**Brand concept**

Gentle. Predictable.

**Lotus flower** has been chosen as a key motive
- Lotus needs water like Dilapan-S
- Flower opening symbolizes dilation / opening of cervix
- Doctors can be sure that, as the flower will bloom in its time, Dilapan-S will dilate the cervix in predicted time.
Induction of labor / IOL

Communication strategy

• In labor induction DILAPAN-S mimics (promotes / supports) physiological processes of the labor.

• It plays the role of active promoter.

• Generally * is recommended to focus on unique combination of efficacy, safety and patient satisfaction

• DILAPAN-S is gentle
  = safe / eliminating safety risks and challenging situations
  = comfortable for patients / offering high patients satisfaction

• DILAPAN-S is predictable
  = effective
  = predictive in expected time frame (one-time application + overnight)

* DILAPAN-S benefits have to be identified and adapted based on methods being used
Induction of labor / IOL

Communication strategy

**Dilapan-S®**

**Efficacy**
- Significant Bishop score increase$^{2-11}$ and vaginal delivery rate up to $80\%$ $^{2,3,4}$
- Spontaneous vaginal delivery with no pharmacological intervention up to $20\%$ $^{2,3,5-8,11}$
- Suitable for VBAC $^{2,3,6,10}$

**Safety$^{2-11}$**
- No hyperstimulation or fetal pathology during cervical ripening
- No infectious complications related to the use of Dilapan-S®
- No limitation related to mother's gestational age and/or comorbidities

**Patient satisfaction**
- Low rate of uterine contractions during cervical ripening $^{2,3,5-8,10,11}$
- Up to $90\%$ of women can relax or sleep during cervical ripening $^{5-8}$
- Minimising of vaginal examination during cervical ripening

**Cost-effectiveness**
- Potential prevention of C. sections in high-risk groups of patients $^{2,3,5-8,10,11}$
- Out-patient regimen (home cervical ripening) for low-risk groups of patients $^{2,3,4}$
- Saving time of health care professionals thanks to one-time application and no need of continuous CTG monitoring $^{12}$

**Unique combination of efficacy, safety and patient satisfaction**
- For clinicians helps to minimise safety risks while maintaining high efficiency $^{2-8}$
- For mothers ensures gentle and predictable cervical ripening and promotes natural vaginal delivery $^{2,11}$
- For health care providers offers reduction of overall healthcare cost $^{2,3,4}$

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*Image of a baby and a lotus flower*
Termination of pregnancy / TOP
Communication strategy

• In cervical preparation prior to termination of pregnancy, **Dilapan-S prepares the cervix, but doesn’t have any abortion potential.**

• It plays just **auxiliary role** (compare with cervical ripening!!)

• Focus on late 1\(^{st}\) and 2\(^{nd}\) trimester surgical abortions

• Emphasize
  – Efficacy
  – Predictability
  – Safety / no challenging situations
  – Consistency of action
  – Suitability for same-day procedure
  – Guidelines recommendations
Termination of pregnancy / TOP 

Dilapan-S key messaging

• Updated SFP guidelines evaluates DILAPAN-S as the best product in its class of osmotic cervical dilators.
  – Compared to laminaria, Dilapan-S™ achieves cervical dilation in a shorter timeframe and rapidly swells to 3–4 times its initial diameter in situ.
  – Compared with the number of laminaria, approximately half the number of Dilapan-S™ is needed because of the increased dilation achieved by the former.
  – The greatest limitation of laminaria use for cervical preparation is the time required to achieve dilation, usually necessitating a 2-day abortion procedure. Faster acting synthetic dilators were developed to enable D&E to be performed in 1 day.

• Despite the fact that new clinical data with misoprostole has come in past decade, DILAPAN-S represents a gold standard for cervical preparation prior D&E procedure in second trimester thanks to its predictability, efficacy and safety.

• DILAPAN-S is fast acting synthetic osmotic dilator being developed to enable same day D&E procedure in late first and second trimester.

• In comparison with misoprostole, DILAPAN-S offers higher efficacy and better predictability enabling to avoid challenging situations or failed abortions in same day D&E procedure in second trimester.

• Patients and physicians can benefit from combination of DILAPAN-S and misoprostole before D&E procedure in late second trimester.
Termination of pregnancy / TOP
Dilapan-S key messaging

Further attributes, which can be emphasized when selling:

- In comparison with Hegar dilators, gradual non-traumatic dilation significantly reduces the risk of cervical injury and suture repair, and preserves full functionality of the cervix for the future pregnancy.
- Dilapan-S has been used effectively in a broad number of indications.
- Used throughout the world in over 30 countries.
- Dilapan-S has been shown to be safe to use for over 12 years.
- 36 month shelf-life.
- Biocompatibility - Dilapan-S has and continues to undergo strict test procedures to verify that it is compatible with human tissue and for human use.
- Time savings of HCPs
- Sterilised by gamma irradiation. No concerns with residual sterilization products (ethylene oxide as laminarias can have)
DILAPAN-S

Final quiz

Part 3
In cervical ripening, Dilapan-S is better than prostaglandines because:

A/ vaginal delivery rate is higher

B/ doesn’t cause uterine hyperstimulation

C/ is faster
In cervical ripening, Dilapan-S is better than prostaglandines because:

A/ vaginal delivery rate is higher

B/ doesn’t cause uterine hyperstimulation

C/ is faster
Which of the following products has the lowest predictability:

A/ dinoprostone

B/ Foley catheter

C/ Dilapan-S

D/ misoprostol
Quiz / part 3

Question 2

Which of the following products has the lowest predictability:

A/ dinoprostone

B/ Foley catheter

C/ Dilapan-S

D/ misoprostol
Can be gentleness used as a Dilapan-S benefit against dinoprostone? Explain how.

A/ YES

B/ NO
Can be gentleness used as a Dilapan-S benefit against dinoprostone? Explain how.

A/ YES. No or low rate of systemic side effects, no uterine hyperstimulation, women can better rest or sleep during cervical ripening, …

B/ NO
For how many hours has Dilapan-S to be inserted to dilate the cervix for surgical termination of pregnancy in late 1st trimester:

A/ 4 hours

B/ 6 hours

C/ 8 hours

D/ during the night
Quiz / part 3
Question 4

For how many hours has Dilapan-S to be inserted to dilate the cervix for surgical termination of pregnancy in late 1\textsuperscript{st} trimester:

A/ 4 hours

B/ 6 hours

C/ 8 hours

D/ during the night
Based on Instruction for use, Dilapan-S couldn’td be left inserted in the cervix longer than:

A/ 12 hours

B/ 24 hours

C/ 36 hours

D/ not defined, it is up to doctor’s decision
Based on Instruction for use, Dilapan-S couldn’t be left inserted in the cervix longer then:

A/ 12 hours

B/ 24 hours

C/ 36 hours

D/ not defined, it is up to doctor’s decision
What are Dilapan-S key benefits vs dinoprostone? Specify at least 3.
What are Dilapan-S key benefits vs dinoprostone? Specify at least 3.

- Lower uterine contraction
- No risk of fetal distress
- No pharmacological side effects
- Better women’s convenience
- No warnings / contraindications
- Use in women with C. section in medical history
- One-time administration
- No need of specific storage conditions
- …
Is it recommended to add misoprostol to Dilapan-S to reach better cervical preparation prior to termination of pregnancy?

A/ YES

B/ NO
Quiz / part 3

Question 7

Is it recommended to add misoprostol to Dilapan-S to reach better cervical preparation prior to termination of pregnancy?

A/ YES

Routine use of adjunctive buccal misoprostol in addition to osmotic dilators is not recommended before 16 weeks' gestation but may be considered when difficult cervical dilation is anticipated or at later gestational ages.

B/ NO
Dilapan S shelf-life is:

A/ 24 months

B/ 36 months

C/ 48 months
Quiz / part 4

Question 8

Dilapan S shelf-life is:

A/ 24 months

B/ 36 months

C/ 48 months
Thank you for your attention