**DILAPAN-S key take away messages**
**from recent clinical trials and related publications**

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## CLINICAL TRIALS / EVIDENCE

### 1. RCT SOLVE / J. Gupta, UK

- Women undergoing cervical ripening with DILAPAN-S have similar vaginal delivery rates compared to dinoprostone but with fewer instances of uterine tachysystole, hyperstimulation and adverse effects on the fetus.
- More women in the DILAPAN-S group reported better satisfaction in terms of ability to perform their desired daily activities such as walking, dressing, hygiene, shower, ability to sleep, relax, and reported less frequent and lower intense uterine contractions as well as lower pain scores both within the insertion procedure and during the ripening period.
- There was a lower need for re-insertion of DILAPAN-S, by approximately 10 %.
- The trial indicated DILAPAN-S capability to prevent or minimize risk of complications and serious adverse reactions.
- Significantly less women needed analgesia during the cervical ripening process in the DILAPAN-S group, strong opioid analgesics in particular.
- Mean number of 4.7 dilators being inserted for 19 hours in average enabled progress of about 3.2 points in Bishop score when assessing the favorability of the cervix for labor.
- Intrauterine growth restriction and reduced fetal movements represent a group of women with reduced fetal reserve where DILAPAN-S would be a benefit as it is associated with a lower risk of uterine hyperstimulation.
- This would suggest that DILAPAN-S could also be used for cervical ripening as an outpatient procedure.
- Majority of women in the DILAPAN-S group underwent amniotomy after cervical ripening which confirms DILAPAN-S predictability and provides an opportunity to schedule IOL procedure more properly.
- Due to demands on the clinical service not all women were able to receive a timely amniotomy once a favorable cervix had been achieved, potentially pausing or reversing the physiological process of cervical ripening.

### 2. RCT COMRED / A. Saad, US

- DILAPAN-S is fully comparable to low-dose oral misoprostol in vaginal delivery rates (VD, VD24, VD36) while offering a better safety profile and superior maternal satisfaction.
- Vaginal delivery rate within 24 hours was fully comparable; this outcome confirms that “speed of action“ is related to IOL clinical protocol rather than to the method of cervical ripening. DILAPAN-S offers the same “speed of action“ to complete vaginal birth as low-dose oral misoprostol.
- Uterine tachysystole with NRFHT during cervical ripening was lower in DILAPAN-S group.
- Unlike misoprostol, no newborn with 5 minutes Apgar score <7 and Cord arterial pH <7.1 occurred in DILAPAN-S cohort, which confirms DILAPAN-S safety benefits.
- Unlike DILAPAN-S, almost 60 % of women in the misoprostol group didn´t receive the planned dosage of the agent due to complications associated with its use. Cervical ripening with DILAPAN-S is more predictable and therefore allows enhanced IOL scheduling.

- Mothers induced by DILAPAN-S reported significantly lower pain when compared to oral misoprostol.
- While women in DILAPAN-S group were allowed to ambulate, women in the misoprostol group underwent continuous CTG monitoring.

**3. <u>RCT DILAFOL / A Saad, US</u>**

- With 81 % of vaginal delivery rate DILAPAN-S represents a highly effective cervical ripening agent. The results indicated a trend towards more vaginal deliveries and a lower C. section rate in DILAPAN-S group vs Foley bulb.
- Almost 50 % of women delivered within 24 hours from device placement.
- DILAPAN-S achieved 87 % success rate in the first round of cervical ripening while 5 pieces for 13 hours were used.
- Low occurrence of adverse events confirmed DILAPAN-S favorable safety profile.
- DILAPAN-S is superior to a Foley balloon in maternal satisfaction during cervical ripening. Induced women were significantly more satisfied in terms of the possibility to sleep, relax and perform daily activities without limitations.
- Post-ripening cervical assessment was based on cervical dilation (>3 cm) and effacement (>60 %) rather than on whole Bishop score reached.

**<u>b/ Secondary analysis of DILAFOL trial: Effect of hygroscopic osmotic dilator versus Foley balloon on cesarean delivery rates: A Bayesian analysis / A Saad, US</u>**

- DILAPAN-S has a higher probability of decreasing cesarean rates in patients undergoing pre-induction cervical ripening than Foley balloon.
- The savings from reduced cesarean section rates and improved patient satisfaction may make DILAPAN-S cost-effective compared to the Foley balloon despite higher product-related costs.

**4. <u>RCT HOMECARE / A. Saad, US</u>**

- Outpatient cervical ripening with DILAPAN-S is as effective and safe as in the hospital setting.
- DILAPAN-S outpatient cervical ripening significantly reduces the length of hospital stay, which can help to reduce staff time requirements and may have a positive impact on the hospital budget.
- Out-patient use of DILAPAN-S for cervical ripening resulted ina significant reduction in the need for analgesia.
- In addition to the superior maternal satisfaction with DILAPAN-S, as seen in previous RCTs, outpatient cervical ripening may further improve the maternal experience and associated level of satisfaction.
- Only 4 out of 166 women (2.4%) in the outpatient group returned to hospital prematurely, confirming DILAPAN-S as a highly predictable cervical ripening agent with easy scheduling.

**<u>b/ Secondary analysis of HOMECARE trial: Economic evaluation of outpatient vs. Inpatient cervical ripening using DILAPAN-S prior to induction of labor / E. Avritscher, US</u>**

- The reduction in hospital stays and reduced staff time requirements associated with DILAPAN-S outpatient cervical ripening resulted in a significant 11% reduction inhospital costs.

**5. <u>International observational Dilapan-S e-registry / J. Gupta, UK</u>**

- No adverse neonatal outcome with DILAPAN-S.
- Use of Dilapan–S did not lead to serious maternal or neonatal adverse events.
- Insertion time up to 12 hours lead to vaginal delivery rate 76,6%.

- Mean number of used dilators to achieve successful outcome of cervical ripening was 4.
- Consistent Bishop score gain (+3,6) across all types of induced women.
- 95% of women evaluated insertion as fully acceptable.

6. **USE-DILAPAN / A. Abuhamad, US**

- The trial confirmed that most of DILAPAN-S swelling effect „in situ" is reached already in initial 6-8 hours after insertion.
- The trial implies that there could be a potential to shorten insertion interval up to 6-8 hours from the currently recommended 12 hours insertion, which would further support DILAPAN-S versatility a flexibility.

7. **Kingston Maternity Hospital; Dilapan-S adoption into the IOL clinical practice. Case report / K. Johnson, UK**

- Adoption of DILAPAN-S into the clinical practice helped to improve IOL clinical outcomes, such as significant reduction of using analgesia during the IOL process by 70%, time reduction to achieve ARMable status by 10 hours and offers potential annual cost savings around 200k GBP for 6000-births unit.

8. **Cervical ripening after cesarean section: A prospective dual center study comparing a mechanical osmotic dilator vs. prostaglandin E2 / J.T.Koenigbauer, Germany**

- With the cesarean section rate raising, the trial of labour appears as a viable option to counteract the trend.
- DS is viable, effective, in-label option, without the risk of uterine hyperstimulation for IOL of woman with previous CS.
- Induction of labour with DILAPAN-S in VBAC women led to 52% successful vaginal delivery rate.

9. **Experimental comparison of properties of natural and synthetic osmotic dilators / T. Drunecky, Czech republic**

- Synthetic dilators Dilapan-S and Dilasoft are superior to natural Laminaria;
    - Reach higher maximum diameter
    - Act faster
    - Are more consistent and due to that predictable
    - Are able to expand against force three times more
- The results support clinical observations that synthetic dilators are more suitable and preferable option for cervical dilation and ripening. Fewer synthetic dilators are needed for shorter insertion time to achieve the same effect.

## CLINICAL GUIDELINES

10. **NICE Guideline; Inducing labour (NG207), November 2021 / UK**

- DILAPAN-S is recommended by NICE GL for routine use in induction of labour.
- DILAPAN-S is recommended for cervical ripening in the outpatient setting.
- Mechanical methods should be always used whenever pharmacological methods are not suitable or the woman chooses to use a mechanical agent.
- Mechanical methods are recommended across a broad spectrum of IOL indications, for example, induction of labour for all cases in >41+0 weeks of gestations.
- Guidelines emphasize maternal choice as a crucial part of the decision-making process and call healthcare professionals to discuss methods for induction of labour with expectant mothers.

- Guideline encourages discussion with women regarding risks and benefits of each method, i.e. safety benefits of mechanical methods and safety risks of pharmacological methods.
- NICE released *Information for the public*, mentioning the care mothers should expect in their IoL and how to make the informed decisions.

**11. <u>Mechanical methods for induction of labour; European consensus, 2021</u>**

- International european consensus recommends mechanical methods, incl DILAPAN-S for routine use in induction of labour.
- Safety profile, decrease need of maternal-fetal monitoring, potential cost savings and suitability for out-patient cervical ripening are listed between potential benefits.

**12. <u>Induction of Labour. Guideline of the DGGG, OEGGG and SGGG Societies; (No.015-088) / Germany</u>**

- The Guideline recommends Dilapan-S for routine use in cervical ripening / IOL.
- Along newly released NICE GLs these are another respected european clinical guidelines, which point out the potential benefits of mechanical methods and DILAPAN-S over pharmacological, incl. decrease risk of uterine hyperstimulation and no mandatory CTG use.
- Inducing labour is a medical intervention, which is why providing information and advice/consultation with an individual risk-benefit analysis is necessary. The aim when consulting with the patient is to arrive at a joint decision which is supported by the pregnant woman.
- Overwhelming majority of affected pregnant women meet the requirements for an attempt do deliver vaginally and must be informed about that.

## COST-EFFECTIVENESS

**13. <u>DILAPAN-S or PROPESS for inpatient induction of labour: A UK cost-consequence model / K. Walker, UK</u>**

- The model compares two NICE recommended cervical ripening agents; DILAPAN-S and dinoprostone vaginal insert (PROPESS)
- Use of DILAPAN-S was assosiated with a significant reduction in staff time requirement, primarilly due to reduced monitoring requirement, lowe rate of hyperstimulation and decrease use of analgetics. This can help to reduce load on maternity units.
- Adoption of DILAPAN-S is likely to be cost-neutral, therefore adding DILAPAN-S to UK clinical practice is not expected to increase hospital spending. With in average 5 dilators used for cervical ripening, DILAPAN-S cost is higher than Propess in the UK. However the model shows that cost of CRA represents approximately 1% of total IOL care costs and that other parameters such as staff time savings play more important role in cost-effectiveness evaluation.

## DILAPAN-S MESSAGING

*Please find below advanced example of DILAPAN-S messaging, which could be used while selected topic is discussed with HCP. Majority of them are based on the above key take away messages. An idea is to offer you broader spectrum of possible product communication. Please always follow your local regulatory requirements to localize into your communication strategy.*

***„Why should I prefer DILAPAN-S prior to pharmacological cervical ripening?"***

- DILAPAN-S is fully comparable to pharmacological methods in vaginal delivery rate, while offering better safety profile and superior maternal satisfaction.[1,2]
- First round cervical ripening success rate with DILAPAN-S is around 80%. In SOLVE trial the rate was approximately by 10% higher than with Propess.[1,2,3]
- DILAPAN-S significantly reduces staff time requirement and can help to decrease load on maternity units. Its non-pharmacological cervical ripening brings predictability into the IOL procedure. It allows to improve schedulling of daily work at maternity unit and overall maternal care. [13]
- Additional reduction in staff time requirement and hospital costs can be reached by DILAPAN-S use in outpatient cervical ripening. [4b]
- DILAPAN-S cervical ripening does not require special care such as repeated CTG and brings flexibility to your induction patient pathway. [13]
- NICE GL stated that mechanical methods should be always used whenever pharmacological methods are not suitable or the woman chooses to use a mechanical agent.[10]
- Induction with DILAPAN-S helps to decrease a need of analgetics, incl. strong opioids.[1,7]
- DILAPAN-S offers to solve the issue of PGEs´ uterine tachysystole, incl. those with NRFHR.[1,2,3,4]
- DILAPAN-S improves maternal satisfaction during cervical ripening, incl. pain decrease reported by mothers.[1,2,3]
- Safety profile, decrease need of maternal-fetal monitoring, potential cost savings and suitability for out-patient cervical ripening are listed between potential benefits of mechanical methods in European consensus statement.[11]
- DILAPAN-S represents an universal product which is suitable for almost all induced women.

***„Why should I prefer DILAPAN-S prior to Foley balloon?"***

- DILAPAN-S offers superior maternal satisfaction compared to Foley balloon. [3]
- DILAPAN-S has a higher probability of decreasing cesarean rates in patients undergoing pre-induction cervical ripening than Foley balloon. The savings from reduced cesarean section rates and improved patient satisfaction may make DILAPAN-S cost-effective compared to the Foley balloon despite higher product-related costs. [3b]
- For induced women, DILAPAN-S is more comfortable to wear as it doesn´t protrude from the introitus. [3]
- DILAPAN-S is fully CE marked and FDA approved for its use in induction of labour.
- Due to the different mode of action, softening of the cervical tissue representing one of the most important parameters of successful cervical ripening is visibly higher when DILAPAN-S is used.
- For those hospitals, which keep Foley balloon under the traction: DILAPAN-S doesn´t require repeated checking of its placement as Foley balloon to keep it under traction and therefore may offer reduction in staff time requirements.

***„I would like to improve cervical ripening success rate"***

- Recent randomised clinical trials indicate that first round cervical ripening success rate with DILAPAN-S is around 80%. In SOLVE trial the rate was approximately by 10% higher than with Propess.[1,2,3]
- DILAPAN-S works differently from other methods, so a ripe cervix will apprear different too. The cervix will be soft, stretchy and dilated. Can happens that the cervix will appear less effaced than with other methods prior to ARM. However it is soft and stretchy, so cervical tissue compressed by fetal head will tend to efface further.

***„What vaginal delivery rate should I expect from DILAPAN-S?"***

- In five clinical trials with in total 1312 women induced by DILAPAN-S (SOLVE, COMRED, DILAFOL, HOMECARE, clinical registry), vaginal delivery rate ranged from 63% to 81%, depending on share of nullips vs multips and clinical protocol used.[1,2,3,4,5]
- In SOLVE trial, women undergoing cervical ripening with DILAPAN-S have similar vaginal delivery rates compared to dinoprostone but with fewer instances of uterine tachysystole, hyperstimulation and adverse effects on the fetus.[1]
- In COMRED trial, DILAPAN-S was fully comparable to low-dose oral misoprostol in vaginal delivery rate, while offering better safety profile and superior maternal satisfaction.[2]
- DILAPAN-S is non-inferior to Foley balloon in vaginal delivery rate, while showing trend to more vaginal deliveries by 5,2%.[3]

***„Vaginal delivery within 24 hours is an important parameter for our preference in use"***

- In DILAFOL trial, 50% of women delivered within 24 hours from device placement.[3]
- In COMRED trial, VD24 rate was fully comparable between DILAPAN-S and low dose oral misoprostol; 41.1%, resp. 38.2%. DILAPAN-S offers the same „speed of action" to complete vaginal birth as pharmacological agent.[2]
- In HOMECARE trial, VD24 rate from admission was 70.1% in outpatient group compared with 50.3% in inpatient group.[4]
- The USE-DILAPAN trial implies that there could be a potential to shorten insertion interval up to 6-8 hours from the currently recommended 12 hours insertion, which would further support DILAPAN-S versatility a flexibility.[6]

***„Maternal and neonatal safety is mandatory for our hospital"***

- Non-pharmacological cervical ripening with DILAPAN-S will help you to solve an issue of frequent uterine tachysytole and minimize risk of hyperstimulation with FHR changes.[1,2,3,4,5,10,11]
- NICE GL encourages discussion with women regarding risks and benefits of each method, i.e. safety benefits of mechanical methods and safety risks of pharmacological methods.[10]
- Trials comparing DILAPAN-S to dinoprostone (SOLVE) and low dose oral misoprostol (COMRED) identified DILAPAN-S safety benefits to pharma approaches.[1,2]
- In five clinical trials with in total 1312 women induced by DILAPAN-S (SOLVE, COMRED, DILAFOL, HOMECARE, clinical registry), low occurence of adverse events were reported, which confirms DILAPAN-S favorable safety profile.[1,2,3,4,5]
- Mothers induced by DILAPAN-S reported lower pain when compared to dinoprostone or low dose oral misoprostol.[1,2]
- In COMRED trial, uterine tachysystole during cervical ripening and uterine tachysystole with non-reassuring fetal heart changes during labour were significantly lower in DILAPAN-S group when compared with oral misoprostol.[2]

- SOLVE trial indicated DILAPAN-S capability to prevent or minimize risk of complications and serious adverse reactions.[1]
- In COMRED trial almost 60% of women induced by low dose oral misoprostol didn´t receive planned dosage due to complications.[2]
- Adoption of DILAPAN-S into the clinical practice helped to improve IOL clinical outcomes, such as significant reduction of using analgesia during the IOL process.[1,7]

***„Our hospital implemented maternal choice as selection criterium of cervical ripening agent and maternal satisfaction is important for us"***

- Non-pharmacological approach with DILAPAN-S minimizes a risk of strong uterine contractions during cervical ripening and improves maternal satisfacton rate.[1,2,3,4,5,7]
- Cervical ripening with DILAPAN-S brings better to superior maternal satisfaction to other cervical ripening agents.[1,2,3]
- DILAPAN-S insertion procedure was evaluated by 95% of women as fully acceptable.[5]
- IN SOLVE trial, reported pain assosiated with cervical ripening agent placement was lower in DILAPAN-S group when compated to Propess.[1]
- DILAPAN-S outpatient cervical ripening can further enhance maternal satisfaction with the product. [4]
- NICE Guideline emphasizes „maternal choice" as crucial part of decision making process and call Healthcare Professionals to discuss methods for induction of labour with expectant mothers.

***„We are facing a significant challenges with staff shortage and overloading"***

- Non-pharmacological cervical ripening with DILAPAN-S is predictable and allows you schedulling.
- DILAPAN-S cervical ripening does not require special care such as repeated CTG and brings flexibility to your induction patient pathway.
- When women can ripen by DILAPAN-S, staff time and resources are made available for other patients with different need.
- UK economic model indicates that adoption of DILAPAN-S into the clinical practice should reduce requirement of midwifery staff time by 2.4 hours per induced woman when compared with dinoprostone vaginal insert.[13]
- Adoption of DILAPAN-S into the clinical practice helped to improve IOL clinical outcomes, such as significant reduction of using analgesia during the IOL process by 70%, time reduction to achieve ARMable status by 10 hours and offers potential annual cost savings around 200k GBP for 6000-births unit.[6]
- In COMRED trial, almost 60% of women induced by low dose oral misoprostol didn´t receive planned dosage due to complications. Whereas women in DILAPAN-S group were allowed to ambulate, those in misoprostol group underwent continuous CTG monitoring.[2]
- HOMECARE trial confirmed DILAPAN-S as effective and save option for out-patient cervical ripening, while offering further reduction of load on maternity unit.[4]

***„We prefer methods recommended by clinical guideline"***

- DILAPAN-S is recommended by many European and US national guidelines, incl. NICE guideline for routine use in induction of labour.[10,12,...]
- Mechanical methods should be always used whenever pharmacological methods are not suitable or the woman chooses to use a mechanical agent.[10]
- Mechanical methods are recommended across a broad spectrum of IOL indications, for example, induction of labour for all cases in >41+0 weeks of gestations.[10]

- NICE GL encourages discussion with women regarding risks and benefits of each method, i.e. safety benefits of mechanical methods and safety risks of pharmacological methods.[10]
- European international consensus recommends mechanical methods, incl DILAPAN-S for routine use in induction of labour.[11]

***„Our hospital offers out-patient cervical ripening"***

- Recently completed randomised trial HOMECARE confirmed that out-patient use of DILAPAN-S remains as effective and safe as in in-patient setting, while significantly shortens hospitalisation time, significantly increases vaginal delivery rate within 24 hours after admission and further improves maternal satisfaction with procedure.[4]
- Secondary analysis of HOMECARE trial identified that the reduction in hospital stays and reduced staff time requirements associated with DILAPAN-S outpatient cervical ripening resulted in significant 11% reduction in hospital costs.[4b]
- DILAPAN-S is recommended by NICE GL for cervical ripening in the outpatient setting.[10]
- With DILAPAN-S, women can ripen at home, while staff time and resources are made available for other patients with different needs.

***„Based on which clinical evidence do you promote DILAPAN-S efficacy, safety and maternal satisfaction?"***

- Since 2018, five big prospective clinical trials (four randomised – DILAFOL, COMRED, SOLVE, HOMECARE and one observational real world data registry) were completed.

***„How many DILAPAN- S pieces should I use to ripen cervix successfuly?"***

- Average number of dilators used in recent DILAPAN-S clinical trials was from 4 to 5.[1,2,3,4,5]
- DILAPAN-S works differently from other methods, so a ripe cervix will apprear different too. The cervix will be soft, stretchy and dilated. Can happens that the cervix will appear less effaced than with other methods prior to ARM. However it is soft and stretchy, so cervical tissue compressed by fetal head will tend to efface further.
- In some clinical trials, post cervical ripening decission to continue in induction procedure was based on cervical dilation (>3cm) and effacement (>60%) than on whole final Bishop score.[2,3,4]