DILAPAN-S product training

Dilapan-S®

Oct 2022

Content

- Introduction of company MEDICEM
- DILAPAN-S introduction
- IOL market overview
- Key competitors
- DILAPAN-S clinical program (past, present, future)
- Communication strategy
- UK ambition and 2022 goals
- DILAPAN-S clinical evidence
- Promomaterials

Made in Czech Republic

Czech Republic

- Located in the “heart of Europe”
- 10.7 million inhabitants / bigger London

BUT

- Footprint in the global perspective

You may know

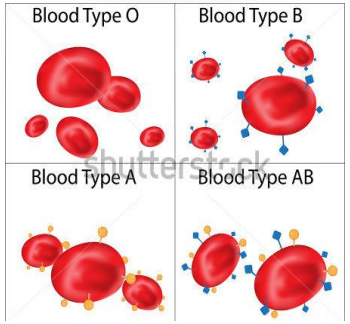
Bata

ROBOT

You may know / Science and medicine

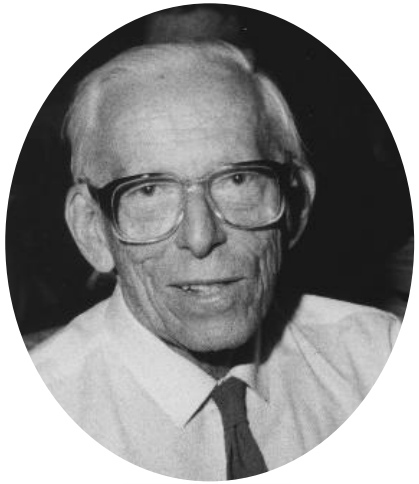
Jan E. Purkyně
Purkinje cells / brain
Co-founder of cytology

Johan G. Mendel
Genetics principles



Jan Jánský
Blood types

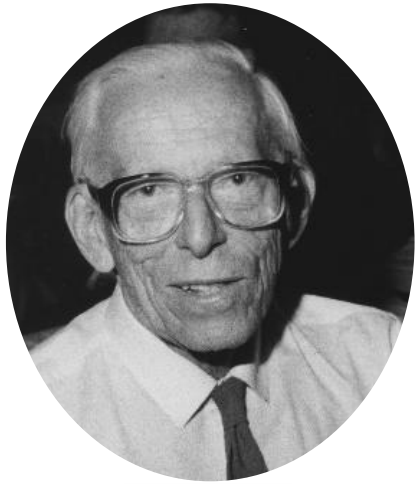
Antonín Holý
Antivirotics
HIV / HBV treatment



Otto Wichterle
Hydrogel soft contact lenses

DILAPAN-S background and heritage

Otto Wichterle
Hydrogel contact lenses



Vladimir Stoy
Co-founder of MEDICEM
Former Chief Scientific Officer MEDICEM

He expanded hydrogel applications
↓
Cervical dilators
↓
Bioanalogic intraocular lenses

Who we are

MEDICEM

- Based in the Czech Republic.

- A biomedical company researching, developing, manufacturing, and commercializing medical devices with unique, proprietary hydrogels for specific clinical applications.
- Deep scientific heritage of hydrogel material development. From cervical ripeners to intraocular lenses.
- Developed more than a dozen products that help patients around the world in the areas of gynecology, ophthalmology, dermatology, wound care and surgery.
- Nowadays fully focused on OBS/GYNE therapeutical field.

- 40+ employees.

MEDICEM Technology – the manufacturer of DILAPAN-S / DILASOFT

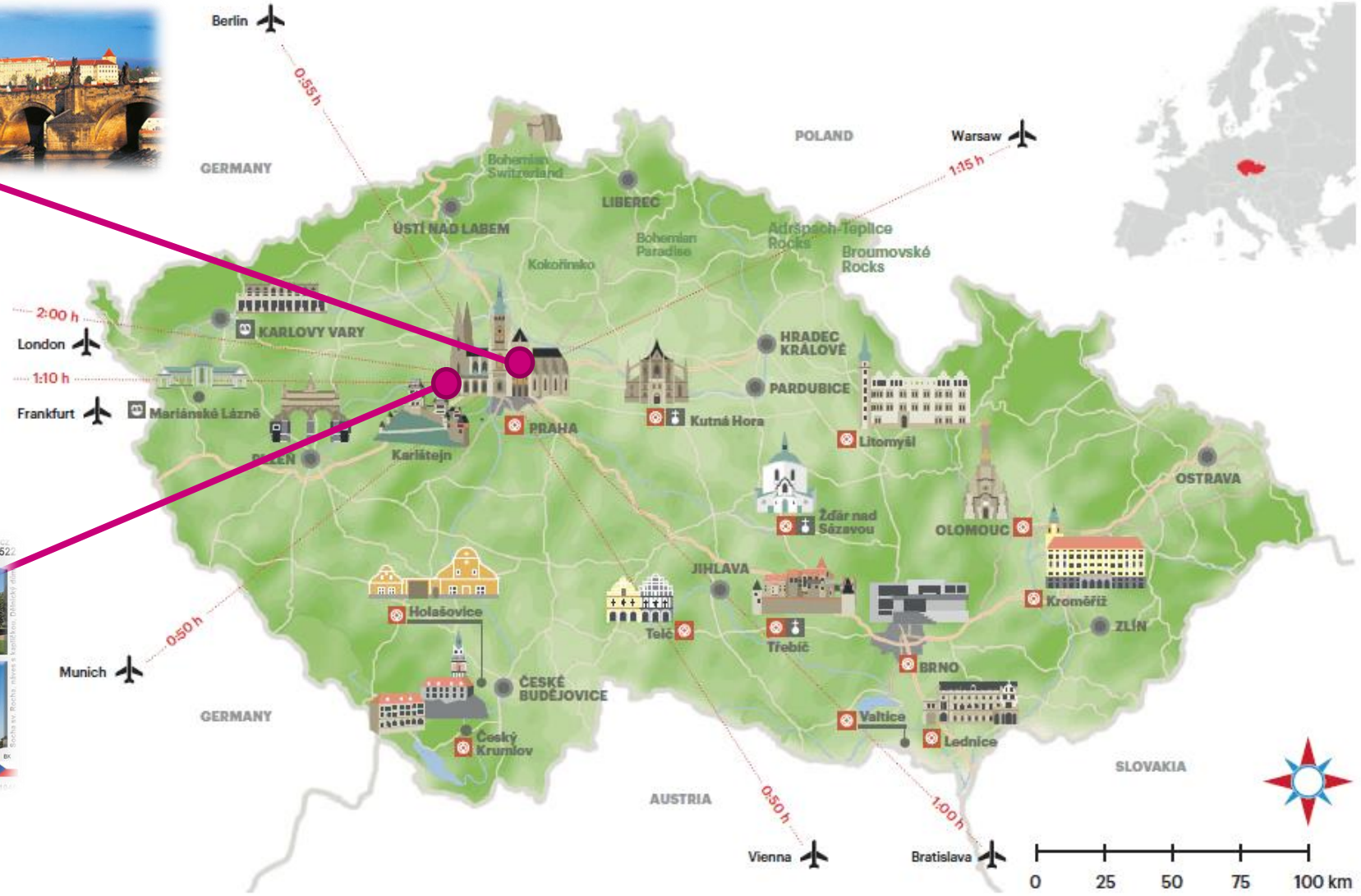
- **Our mission** is to create products that are safe, effective, gentle and reliable for mom, child and physician as well as cost-effective for healthcare system.

- The products provide **unique combination of benefits for both, healthcare professionals and patients.**

Where we are

Prague office

Manufacturing site

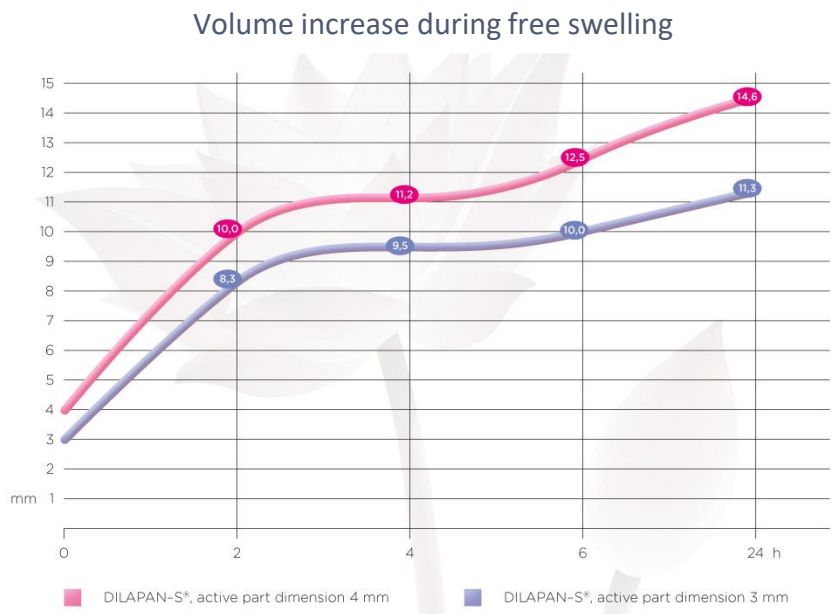


DILAPAN-S introduction

Dilapan-S®

DILAPAN-S / synthetic osmotic cervical dilator

- Non-pharmacological method of cervical ripening / dilation.
- Represents 2nd generation made of a **patented hydrogel AQUACRYL®.**
- The rigid dilator is capable of increasing in diameter by absorbing fluids from the cervical canal.



The principal effect is reached
in the first 4-6 hours
(app. 80% of diameter increasing)

Dilapan-S®

What is hydrogel / hydrogel properties

- A hydrogel is a **crosslinked hydrophilic polymer** that does not dissolve in water. They are highly absorbent yet maintain well defined structures. These properties underpin several applications, especially in the biomedical area. Many hydrogels are synthetic, but some are derived from nature.

    - A **polymer** is a substance or material composed of very largemolecules / macromolecules
        - Natural: fibrin, heparin, hyaluronid acid
        - Synthetic: polyakrylonitrile (hydrogel AQUACRYL)
    - **Hydrophilic** describes things that tend to interact with water in some way.
    - In chemistry and biology a **cross-link** is a bond that links one polymer chain to another. It is used to promote a change in the polymers´physical properties.

- **Hygroscopic;** tending to absorb moisture from the environment
    - = related to feature of material
- **Osmotic;** connected with the process by which a liquid / water moves gradually from one place (part of the body) to another through a membrane. The swelling of the dilator is due to osmotic intake of water.
    - = related to mode of action

Brand name vs generic term to use

- The product belongs to the group of „cervical dilators“ and/or „mechanical ripening products“.
- Clinical papers and guidelines tend not to differentiate mechanical ripeners so much, esp. DILAPAN-S vs laminaria are often listed together as „hygroscopic cervical dilator“.

- However DILAPAN-S hydrogel material is unique and the product represents the best product in its class in terms of efficacy, safety and maternal satisfaction (see publications comparing DS with Lams).

- Long-term ambition is to create a perception of two groups of cervical dilators
  - Synthetic = DILAPAN-S / DILASOFT
  - Natural = Laminaria

Brand name vs generic term to use

- Whenever it is possible, brand name **DILAPAN-S** should be used.
- If generic term is requested, use a term **synthetic osmotic dilator.**
  - „synthetic“ differentiates the product from natural laminaria.
  - „osmotic“ is related to its mode of action. Prefer term „osmotic“ prior to „hygroscopic“ (which rather describes a feature of material).
  - Don´t use „cervical“ if it is clear from the context that cervical ripening is discussed. If not, longer version **synthetic osmotic cervical dilator** can be used.

Example of versions, which shouldn´t be used:

- Mechanical dilator

  (does not differentiate DILAPAN-S from other

  dilators)
- Osmotic hygroscopic dilator

  (prefer „osmotic“ prior to“hygroscopic“)
- Synthetic osmotic hygroscopic cervical dilator *(too long)*

Core indications

1. Induction of labor (IOL)

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

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

A couple of „technical“ facts

- DILAPAN-S is sterilised by **irradiation.**
- Supplied sterile, in peel-open pouches.
- Manufactured in an **ISO 9001 Certified facility.**
- **Fully CE Certified** under the Medical Device Directive.
- **Approved by FDA** for sale in the United States.
- Registered in more then **40 countries** worldwide.

- Packaging: 10 or 25 pcs
- Size
  - 3x55mm (IVF, IUD, hysteroscopy,..)
  - 4x55mm (IOL)
  - 4x65mm (IOL, TOP)

History od DILAPAN-S / DILASOFT

- DILAPAN
  - Represented 1st generation of synthetic osmotic dilators
  - On the market in 80s – 90s of the last century
  - Issue: higher risk of fragmentation

- DILAPAN-S
  - 2nd generation of osmotic dilators made from AQUACRYL® - a patented hydrogel
  - Development initiated in 1994, fragmentation issue overcame
  - Registration: CE mark (1998), FDA approval (2002), Canada (2005), Japan (2007), many local national registrations

- DILASOFT
  - The same hydrogel as DILAPAN-S
  - The dilator is flexible and can be shaped, because of customised production technology (higher hydration of the dilators)
  - Developed on special request of the Japanese market and sold in the Japan since 2010
  - Currently sold only in Japan

CERVICAL RIPENING / INDUCTION OF LABOUR

Dilapan-S®

Introduction to induction of labour

- Approximately 30% / 40% of labours start artificially and need to be induced.
- The trend of inductions is rising – mother comorbidities or baby in risk, elective inductions,..
- Successful labour induction is clearly related to the state of the cervix.
- Approximately 70% / 80% of inductions need cervical ripening.

Induction of labour /2 steps procedure – cervical ripening vs induction

Initial status of the cervix	Cervical ripening Process of softening and opening the cervix before labour starts, which allows to pass a baby through a birth canal.	Labour induction Artificial stimulation of uterine contractions in an effort to have a vaginal birth.
Ripe / favorable	X	→
Unripe / unfavorable	→	→

Successful labour induction is clearly related to the state of the cervix.
Women with an unfavourable cervix, who have not experienced cervical ripening phase before own promotion of uterine contractions, present the greatest challenge with regard to labour induction.

Bishop score / a manner to evaluate whether the cervix is ripe

- Bishop score is usualy used to determine status of the cervix
- Several modifications of **Bishop score** exist;
  - **13 points scale / ** score > 6 represents limit to evaluate the cervix as favourable
  - **10 points scale /** score 5 represents limit to evaluate the cervix as favourable
- Cervical consistency (softening), dilatation and effacement can be perceived as crucial parameters
  - Focus on these can be preferred prior to full BS assessment

Example of 13 points Bishop score

	Factor				
Score	Dilation (cm)	Position of Cervix	Effacement (%)	Station*	Cervical Consistency
0	Closed	Posterior	0–30	–3	Firm
1	1–2	Midposition	40–50	–2	Medium
2	3–4	Anterior	60–70	–1, 0	Soft
3	5–6	—	80	+1, +2	—

*Station reflects a –3 to +3 scale.

Modified from Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:267.

NICE IOL GL / Bishop score of 6 as decision maker

„For women with a Bishop score of 6 or less, offer induction of labour with dinoprostone, misoprostol or mechanical methods.“*

„For women with a Bishop score of more than 6, offer induction of labour with amniotomy and an intravenous oxytocin infusion.“

Dilapan-S®

Inducing labour, NICE guideline (NG 207), 2021

** Text was simplified for purpose of this slide*

CERVICAL RIPENING WITH DILAPAN-S WHAT TO EXPECT

Dilapan-S®

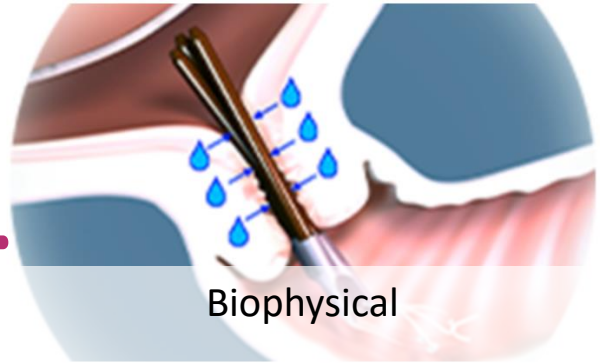
Mode of action

- The dilator increases in volume by absorbing fluids from the cervical tissue.
- DILAPAN-S doesn´t contain any pharmacologically active substance, which could be released during its use.
- Achieved cervical dilation is depending on the length of DILAPAN-S insertion.
- The thin 4mm dilator can expand up to 15 mm over a 12/24 hours period. *
- In labour induction a set of 4 – 5 dilators is usually used to ripen the cervix sufficiently.

* Free swelling; in vitro

Designed specifically to ripen the cervix in three ways

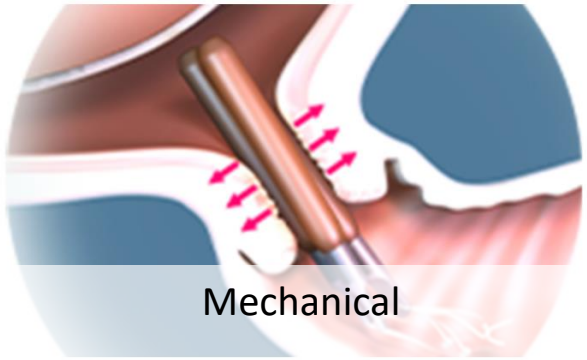
1



Biophysical

Osmotic dehydration of the cervix promotes its softening
→ change in ***consistency*** of tissue

2



Mechanical

Expanding dilators exert radial pressure onto the wall of cervical canal → gradual ***dilatation*** of the cervix

3

Physiological

C**ontinuous pressure** stimulates the release of endogenous prostaglandins
→ ***effacement*** of the cervix

80% First round cervical ripening success rate[1,2]

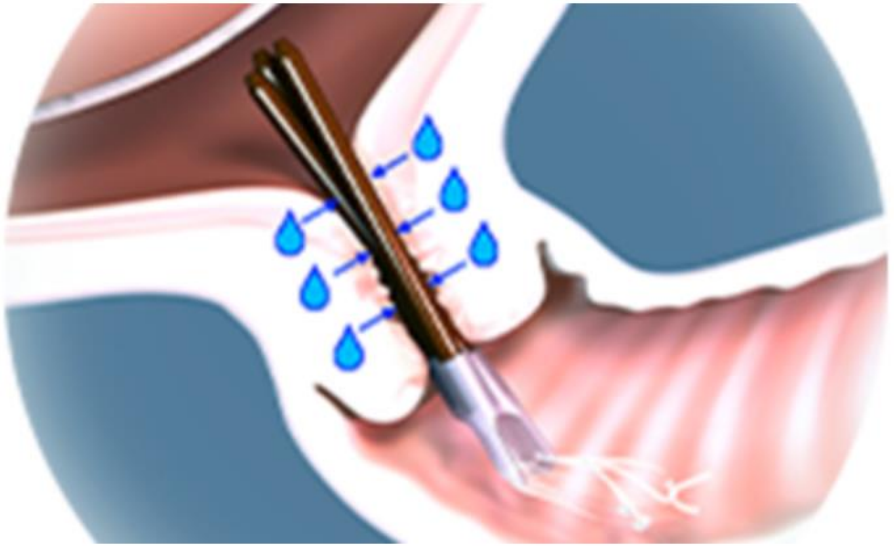
This combined mode of action delivers an unique effect on the cervix when compared to other available methods of cervical ripening.
After DILAPAN-S, the cervix will be notably soft, stretchy and dilated.

Dilapan-S®

1. Saad A. et al. A randomised controlled trial of DILAPAN-S vs Foley balloon for preinduction cervical ripening (DILAFOL trial), Am J Obstet Gynecol, March2019
2. Gupta J. et al. A randomised trial of synthetic osmotic dilator for induction of labor versus dinoprostone vaginal insert (SOLVE), AJOG, March2022

Mode of action / 1. biophysical

Unlike other ripening agents, DILAPAN-S uniquely affects the cervical tissue via osmotic dehydration.



Dilators absorb fluids from cervical tissue via osmosis

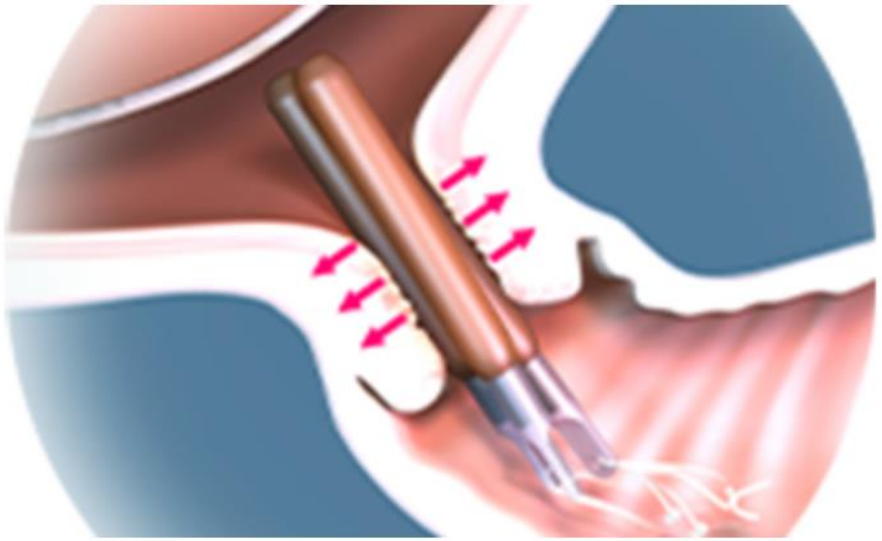
Loss of water causes the cervical tissue to become more flaccid

This leads to change in consistency of the cervix and makes it ‘soft & stretchy‘

Softened tissue further compresses under weight of fetal head, enabling effacement.

Mode of action / 2. mechanical

Whilst expanding in their diameter, DILAPAN-S dilators exert gradually increasing radial pressure against the wall of cervical canal.



Dilators absorb fluids from cervical tissue via osmosis

↓

Absorption of water means dilators expand gradually, whilst remaining turgid

↓

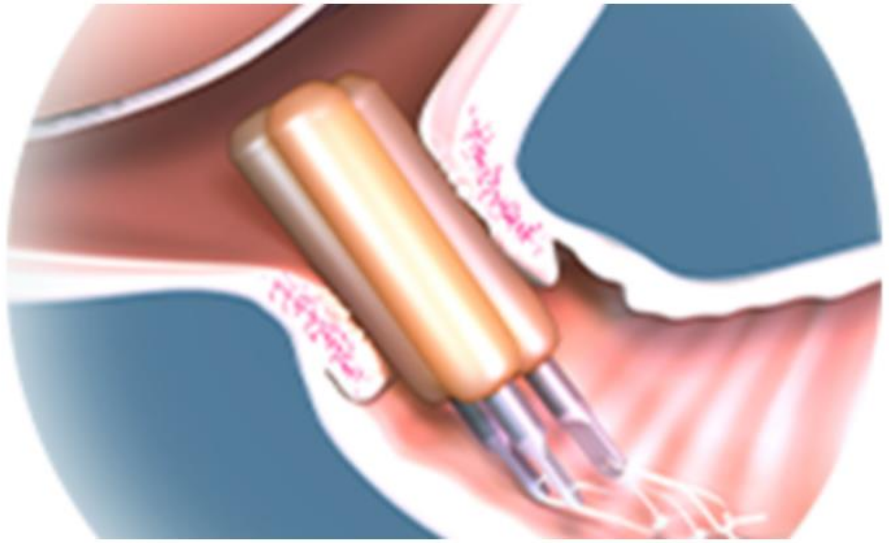
Expanding dilators exert gradual pressure against softened cervix

↓

Gradual softening of cervical tissue allows expansion of dilators, resulting in ***dilatation.***

Mode of action / 3. physiological

Pressure of expanding dilators against the cervical wall stimulates release of endogenous prostaglandins.



Mechanical stretch in the cervical tissue stimulates release of endogenous prostaglandins

Prostaglandins trigger collagen degradation in the cervical tissue

Collagen degradation contributes to tissue reconstruction and ***effacement.***

To summarize

Softened tissue further compresses under weight of fetal head, enabling effacement

Gradual softening of cervical tissue allows expansion of dilators, resulting in *dilatation*

Collagen degradation contributes to tissue reconstruction and cervical *effacement*

The **triple mode of action** of DILAPAN-S supports the cervical maturation in a similar way as in the natural labour itself.

Softening, dilation and stimulation of endogenous prostaglandin release, combined with pressure of fetal head during mobilization*, help to create **a feedback loop to establish a labour.**

Notes

- The cervix may appear less effaced prior to ARM when compared to other methods.
- However, it can be expected that soft and stretchy tissue compresses under the weight of the fetal head will tend to efface further.
- 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]

DILAPAN-S is fully comparable to pharmacological methods in vaginal delivery rate while offering safety benefits and superior maternal satisfaction.[1,2]

Dilapan-S®

1. Gupta J. et al. A randomised trial of synthetic osmotic dilator for induction of labor versus dinoprostone vaginal insert (SOLVE), AJOG, March2022
2. Gavara R. et al. Cervical ripening efficacy of synthetic osmotic cervical dilator compared with oral misoprostol at term, Obs & Gyne, May 2022

How many piece should be used for successful cervical ripening

- For induction of labour, 4mm dilator is indicated. One dilator *in vivo* expands up to approx. 12 mm over 12-15 hours.
- Set of multiple dilators is used to reach successful cervical ripening
  - In Instruction for use is written *„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 healthcare professional and indications“.*
  - Number of dilators depends on a/desired effect (what HCP wants to reach. It is obvious that with 2 pieces can be hardly reached 3 cm dilation), b/ initial status of the cervix (which can affect how many dilators is possible to insert; see below)
  - From EU/US clinical trials is known that set of 4-5 dilators for 12-15 hours is most often used. So **usual number, you should refer on is 4-5.**
  - Occasionaly, in cases of highly unripe cervixes, fewer dilators can be inserted into the cervix. In such cases can be expected that cervical ripening will not be sufficient and second round of dilators will have to be used (see FAQs)

DILAPAN-S
IOL CLINICAL PROGRAM

Dilapan-S®

DILAPAN-S IOL clinical data

- Clinical evidence available till end of Q3/2022
  - UK economic model (UK, K. Walker, 2022); economical analysis comparing DILAPAN-S with Propess – impact on budget and staff time allocation
  - RCT HOMECARE (US, A. Saad, 2022); comparison of in-patient vs out-patient use of DILAPAN-S – length of hospitalisation, efficacy, safety, maternal satisfaction
  - RCT SOLVE (UK, J. Gupta, 2022); H2H comparison with Propess – efficacy, safety, maternal satisfaction
  - RCT COMRED (US, R. Gavara, 2022); H2H comparison with misoprostol – efficacy, safety, maternal satisfaction
  - RCT DILAFOL (US, A. Saad, 2019); H2H comparison with Foley – efficacy, safety, maternal satisfaction
  - International multicenter registry (J. Gupta, 2018) – efficacy (up to / over 12 hrs insertion), safety, maternal satisfaction
  - Prospective multicenter trial (Czech Republic, 2014) – efficacy, safety, maternal satisfaction, VBAC
  - Several small local observational trials (Germany) - VBAC
- Data collected / Comming soon
  - Clinical pilot USE-DILAPAN (US, A. Abuhamad,2022) – capability to swell during first 6-8 hours after insertion
- Ongoing
  - UK registry project - initiated in 2020 with goal to collect data from up to 10.000 induced women
  - US registry project

Dilapan-S®

Please go to DILAPAN-S website / Section for distributors to overview detailed outcomes of completed clinical trials and promotional leaflets available.

COMPETITORS
MECHANICAL METHODS

FOLEY CATHETER & COOK DOUBLE BALOON

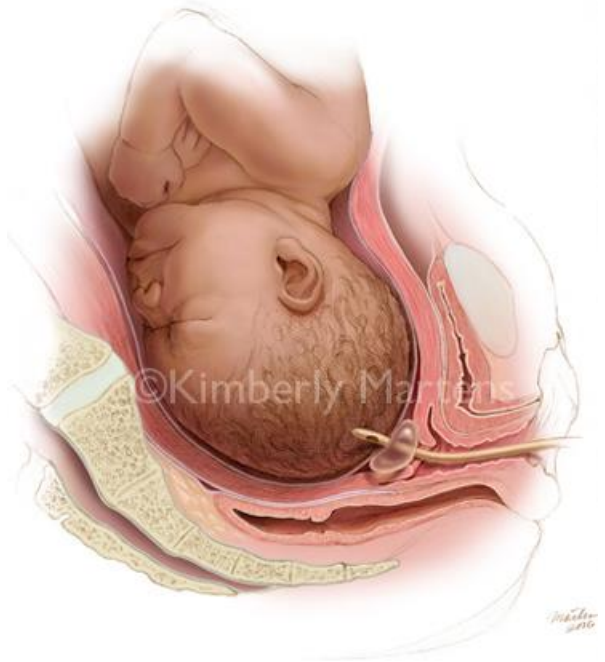
LAMINARIA

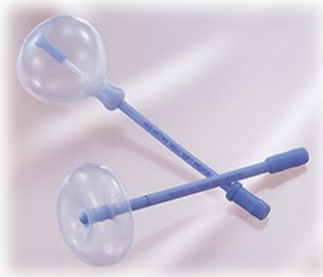
Dilapan-S®

Foley catheter

- Single silicone balloon, gradually inflated with saline after insertion into the cervix and left in situ for 12-24 hours
- Primarily developed as a urinary catheter, so being used for IOL off label
- The product does not have an official IFU – recommendations for its use come from clinical experience
- If spontaneously detached, it can be replaced by new one to reach higher cervical ripening
- Insertion and wearing less comfortable for women
  (quick inflation= pain, traction, taped outside the body)
- Effective and safe
- Low price, approximately 5 EUR per piece

- No active promotion / „selfburning“





Mini Metro / Neo Metro, Japan

COOK double balloon

- Double silicone balloon, MoA similar as Foley balloon, developed and certified for cervical ripening
- Maximum balloon inflation: 80 ml
- Limited time in situ - up to 12 hours
- Effective and safe
- Insertion and wearing less comfortable for women similarly to Foley
- Higher price: 70-80 EUR
- Many contraindications and warnings in IFU:
    - Patients planning to undergo exogenous prostaglandines administration
    - Rupture of membranes
    - Using in women with C. section in medical history

- COOK Medical supports actively the product in some countries

Laminaria

- Similar mode of action as DILAPAN-S®
- 100% natural – made of a sea-grown plant
- Rode size ranges 2-10mm diameters and 60-85 mm length

- Produced by several companies wordlwide
  - The US / MedGyn, Norscan
  - Japan / NIPPON

- When on the market, it is used mainly in termination of pregnancy.

- Except JAPAN there is no feedback from the markets that Laminaria would be used for IOL.

COMPETITORS
PHARMACOLOGICAL METHODS

PGE_2 DINOPROSTONE

PGE_1 MISOPROSTOL

Dilapan-S®

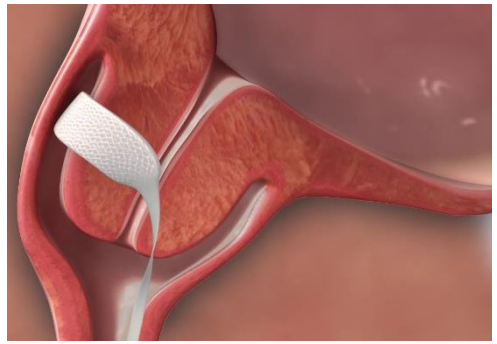
Dinoprostone / PGE2

- **Mode of action:**
  - Prostaglandines cause a/ collagen degradation, which softens the cervix, b/ start smooth muscle contractions, resulting in uterine contractions
- **Indication:**
  - Cervical ripening in patients at or near term
- **Several products / different forms / producers:**
  - Vaginal pessary (Propess)
  - Intracervical gel (Prepidil, Cerviprime)
  - Vaginal tablets (Prostin)
- **Clinically significant contraindication:**
  - Previous Caesarean section
- **Warnings / Precautions:**
  - Cardiovascular, liver, kidney disease, asthma, glaucoma, PROM (premature rupture of membranes)
  - Careful CTG monitoring to detect possible evidence of undesired responses, e.g. uterine hypertonus or fetal distress
    = SHOULD ONLY BE USED IN HOSPITAL
- **Storage condition:**
  - Cold chain – freezer or refrigerator

Dinoprostone vaginal insert / PROPESS (Ferring Pharmaceuticals)

- 10mg dinoprostone vaginal delivery system
- Releasing approximately 0,3mg of dinoprostone/hour
- Maximum insertion time - 24 hours

- Patient should remain lying down for 20-30 minutes after administration
- Price comparable with DILAPAN S or higher
- Storage conditions: in freezer



- Ferring active promotion in EU was terminated in approx. 2020

Dinoprostone intracervical gel / PREPIDIL (Pfizer), CERVIPRIME (Astra Zeneca)

- 3g of intracervical gel containing 0,5mg of dinoprostone
- Repeated administration every 6 hours up to a maximum daily cummulative dossage of 1,5mg

- After insertion of the gel, patient should remain lying down for at least 15-30 minutes
- Gel needs to be stored under continuous refrigeration
- Price varies significantly based on territory

- Not actively promoted by producer(s)

Dinoprostone vaginal tables / PROSTIN (Pfizer)

- 1 vaginal tablet containing 3mg of dinoprostone

- 1 tablet of 3mg to posterior fornix of vagina, another tablet can be applied 6-8 hours later, maximum daily dossage is 6 mg
- Lower dossage can be used (1,5 mg - tablet is cut)
- Storage condition: in refrigerator

Misoprostol /PGE1

- **Mode of action:**
  - Similar to dinoprostone
- **Safety:**
  - Use of PGE1 is associated with a higher risk of uterine tachysystoly / hyperstimulation then PGE2
- **Many products/formulations/producers:**
  - Oral, buccal, vaginal administration
  - Only one product approved in EU for IOL – ANGUSTA
- **Original indication:**
  - Prevention of NSAID induced gastric ulcers
  - In many countries used „off label“, however recommended by GLs for cervical ripening (incl. NICE GL)

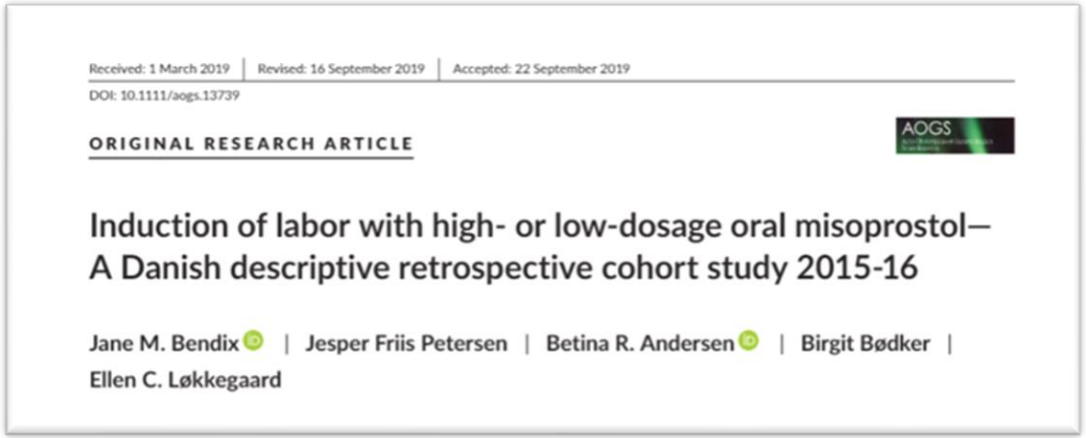
Misoprostol 25 mcg oral tablet / ANGUSTA (Norgine)

- 25 mcg every 2 hours or 50 mcg every 4 hours
- Max daily dosage is 200 mcg

- Marketed in Europe
  - Nordics and France since 2016-2018
  - Other EU countries incl the UK and GER since Q3/2021

Misoprostol 25 mcg oral tablet / ANGUSTA (Norgine)

- No one RCT trial, however registered in EU
  - Denmark „patient compassionate use program“
  - Retrospective evaluation
  - Clinical data with generic miso used for registration
  - Biocompatibility study didn´t confirm biokompatibility with generic miso / FDA refused and requested full clinical program to register in the US



Received: 1 March 2019 | Revised: 16 September 2019 | Accepted: 22 September 2019

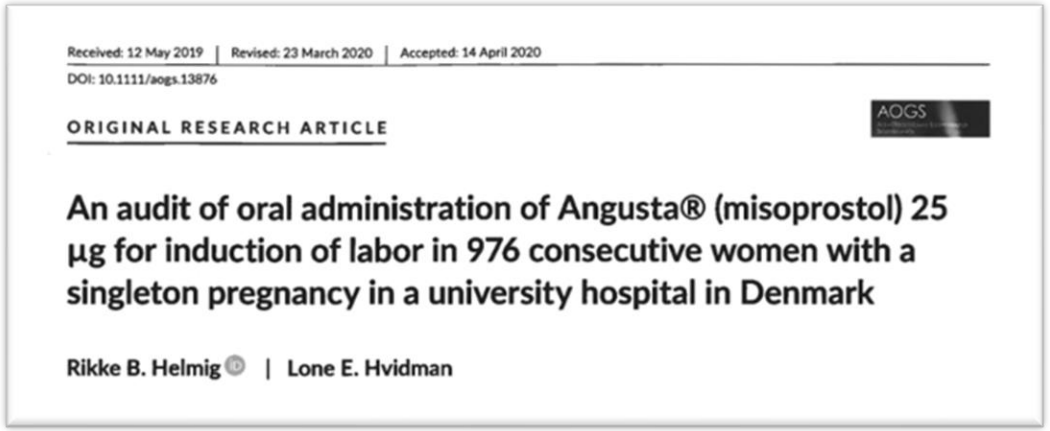
DOI: 10.1111/aogs.13739

ORIGINAL RESEARCH ARTICLE

AOGS

Induction of labor with high- or low-dosage oral misoprostol—A Danish descriptive retrospective cohort study 2015-16

Jane M. Bendix | Jesper Friis Petersen | Betina R. Andersen | Birgit Bødker | Ellen C. Løkkegaard



Received: 12 May 2019 | Revised: 23 March 2020 | Accepted: 14 April 2020

DOI: 10.1111/aogs.13876

ORIGINAL RESEARCH ARTICLE

AOGS

An audit of oral administration of Angusta® (misoprostol) 25 µg for induction of labor in 976 consecutive women with a singleton pregnancy in a university hospital in Denmark

Rikke B. Helmig | Lone E. Hvidman

DILAPAN-S COMPARED TO OTHER METHODS

Dilapan-S®

DILAPAN-S compared to other cervical ripening agents in H2H trials

	Dinoprostone (SOLVE)	Misoprostol (COMRED)	Foley (DILAFOL)
First round successful CR	Comparable, resp+ 10%	NA	Comparable
Vaginal delivery rate	Comparable	Comparable	Comparable
VD 24	DS worse (however affected by clinical protocol)	Comparable	NA
Uterine tachysystole without / with NRFHT during CD	Better	Better	Similar
Complications	Better	Better	Similar
Maternal satisfaction during CR	Signif better	Signif better	Signif better
Pain during CR	Better	Better	Better
Analgetics	Signif better	NA	NA
OXY need	Higher need	Higher need	Comparable

VIDEOS

Dilapan-S®

DILAPAN-S insertion – live video

DILAPAN-S Introduction

Labor Induction with an unfavorable cervix

DILAPAN-S comparison with Laminaria

Dilapan-S®

DILAPAN-S
COMMUNICATION STRATEGY

Dilapan-S®

2022 communication strategy proposal

Adapted for the UK / Europe

Dilapan-S

Basic IOL facts

- IOL rate is gradually increasing and attacks 30% rate nowadays.
- Hospital staff is facing an significant issue of overhelming.
- Big group of midwives, their high level of competencies to manage IOL and „rotation“ in hospitals represent UK specifics
- Role of expectant mothers in decision making process is growing, together with importance of maternal satisfaction with IOL procedure.
- Out-patient (at home) ripening becomes popular between HCPs in several european countries and in the US. Time and budget savings are expected from such approach.
- Updated NICE IOL GL was released in Nov2021. The GL recommends mechanical methods incl DILAPAN-S for IOL.
- Trend of use of mechanical methods is rising. Efficacy is proven to be comparable, while they offer safety benefits. However (not only in Europe) these are still perceived by HCPs as rather alternative option to pharmacological methods then equivalent of even preffered for frontline /routine use. Preference is obvious for specified subindications where use of prostaglandines is challenging (such as VBAC of out-pts ripening).
- ANGUSTA can change changing IOL market significantly!!

NICE guideline [NG207]; Inducing labour

- Updated version released in Nov 2021.
- Significant positive update regarding use mechanical methods and role of mothers in decision making process.
- Along the guideline intended for HCPs, information for the public was released, mentioning the care mothers should expect and make an informed choice.

- NICE GL recommends DILAPAN-S for routine use in cervical ripening. / as a standard IOL procedure
- DILAPAN-S is recommended for outpatient cervical ripening.
- Mechanical methods are recommended across broad spectrum of IOL indications.

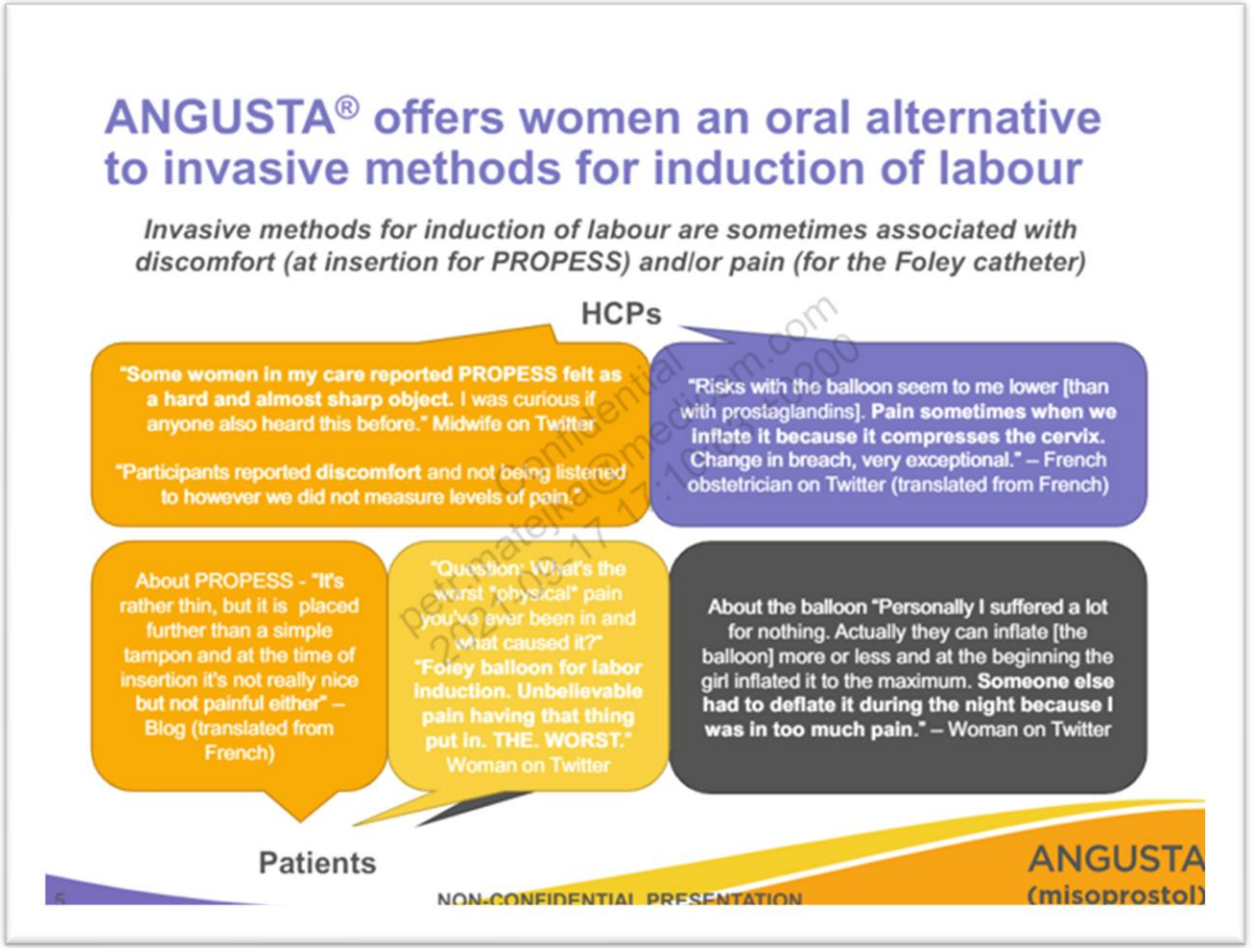
- Guideline emphasizes „maternal choice“ as crucial part of decision making process and call healthcare professionals to discuss methods for induction of labour with expectant mothers.
- Guideline recommends to discuss with women risks and benefits of each method, incl. safety benefits of mechanical methods and safety risks of pharmacological methods (1.3.5).

Competitors

- On the market both pharmacological and mechanical cervical ripening agents are available.

- Balloon catheters
    - Recently (Q1/2022), COOK MEDICAL was aquired by COOPER SURGICAL. Disruption of COOK double balloon promotional activities is assumed.
- PROPESS (dinoprostone vaginal insert)
    - Still market leader and in many countries perceived as standard of care
- ANGUSTA (low dose oral misoprostol)
    - Represents a new player on the market.
    - The product is actively promoted by company (Norgine) and it seems to have a capability to change the market significantly in near future. On next slides you can see example of Angusta communication strategy and how the product has penetrated selected EU market after the launch
    - However product quality issue was reported across Europe in Q2/2022, resulting in product recall and unavailability during Q3/22.

ANGUSTA communication strategy



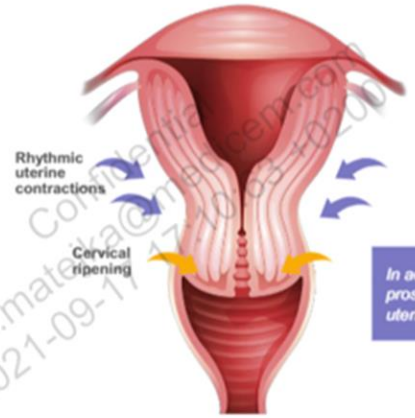
ANGUSTA communication strategy

ANGUSTA® Overview

- **Medical professionals are enthusiastic about using ANGUSTA® given its best in class positioning, label approval and oral delivery**
- ANGUSTA® is a best in class, specially designed drug for the induction of labour.
- Optimal route of administration (oral), dosage and formulation
- ANGUSTA® is a prostaglandin E1 (misoprostol) 25 micrograms oral tablet with an IP protected formulation ensuring high dissolution
- ANGUSTA® is administered orally whilst all competing products in the market are administered intra-vaginal and do not have optimal dose.

ANGUSTA® has a double action on cervical ripening and uterine contraction stimulation

- ANGUSTA® is indicated for induction of labour
- ANGUSTA® is a synthetic analogue of prostaglandin E1 (PGE1) in a 25 µg tablet form, containing misoprostol
- 2 main mechanisms for inducing labour:
  - Cervical ripening
  - Uterine contraction



Prostaglandin E1 is involved in the cervical changes occurring during spontaneous labour, which results in a more soft and pliable cervix.[1,2]

In addition to causing cervical ripening, prostaglandin E1 is known to stimulate uterine contractions.[1,2]

ANGUSTA communication strategy

ANGUSTA® has been used for more than 100,000 women today

- Approved and launched by Azanta in the Nordics and France between 2017 and 2018
- ANGUSTA®'s safety profile has been verified in a compassionate use program including 29,000 women and has now been used by more than 100,000 women giving birth
- ANGUSTA® is approved and will be launched in a number of countries across Europe in the near future

ANGUSTA® and its packaging have been designed specifically for induction of labour

- Ready-to-use tablet of 25 µg
- Blister pack with 8 tablets
- The contents of each package corresponds to the recommended 24-hour max. dosage
- 1 tablet every two hours or 2 tablets every four hours
- A double layer of aluminium foil serves to protect the tablet from moisture
- The dry environment within the aluminium foil blister ensures the chemical stability of misoprostol

Misoprostol is chemically unstable at room temperatures outside the packaging. In such unfavourable conditions outside the double-layer foil blister, misoprostol will degrade into inactive products.

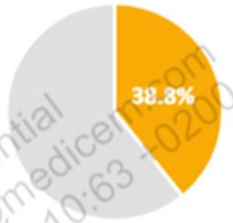
ANGUSTA communication strategy

ANGUSTA® is effective at inducing labour and women prefer oral induction

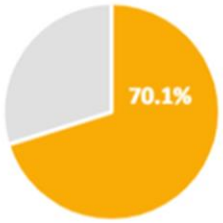
- Low dose oral misoprostol and ANGUSTA® have been widely studied in randomised controlled trials and open-label real-world studies[9-19]
- ANGUSTA® is an effective method of inducing labour leading to vaginal birth[8-11]
- ANGUSTA® is the only registered option for women who prefer oral option

ANGUSTA® – clinical experience

More than 3 out of 4 women had a spontaneous vaginal delivery after use of 25µg ANGUSTA®[18]



38.8% of women gave birth within 24 hours[18]

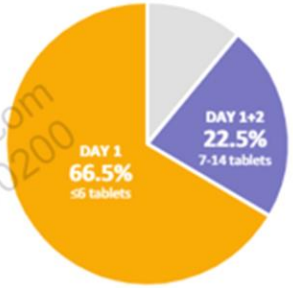


70.1% of women gave birth within 48 hours[18]

ANGUSTA communication strategy

ANGUSTA® – clinical experience

More than 7 out of 10 women were induced in an outpatient regimen[18]*



2 out of 3 women in the outpatient regimen only took ANGUSTA® on Day 1[18]*

* ANGUSTA® should only be administered by trained obstetric personnel in a hospital setting where facilities for continuous fetal and uterine monitoring is available and the cervix should be assessed carefully before product use.[3]

ANGUSTA (misoprostol)

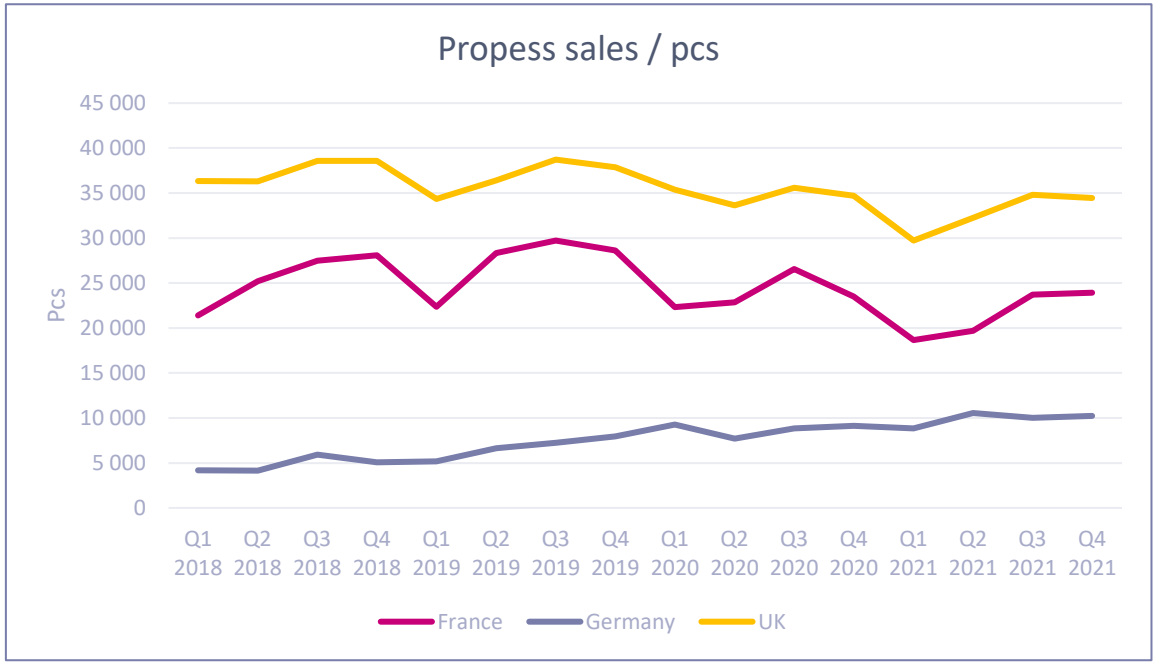
Top 5 reasons to choose ANGUSTA®

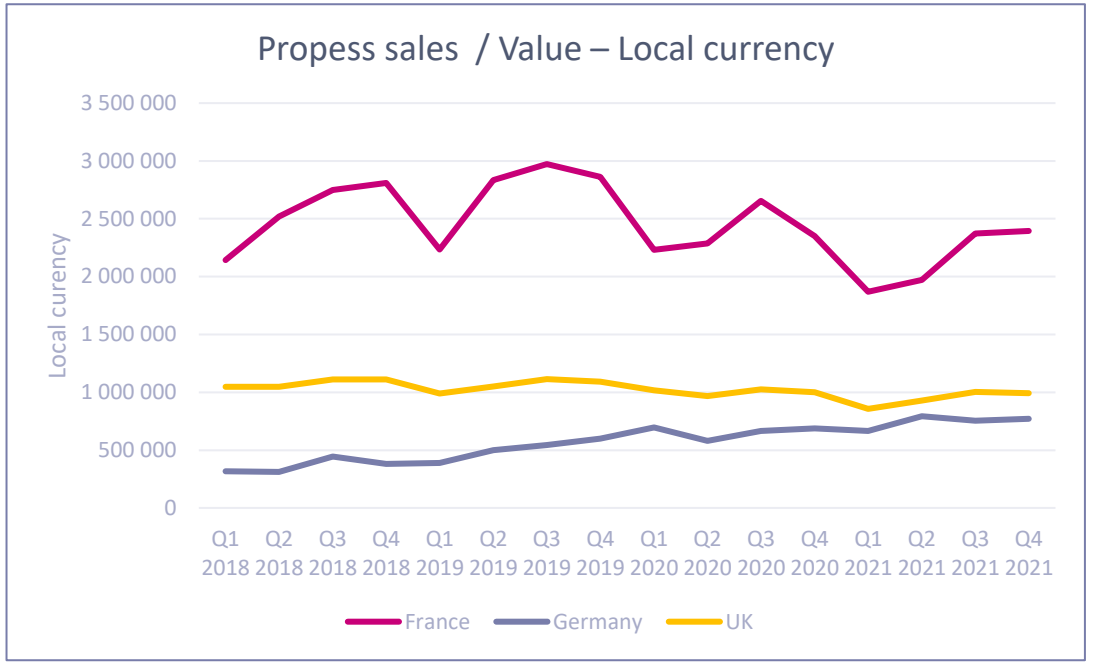
1. **Women prefer oral induction**
   More than 4 out of 5 would use oral misoprostol again for future labour.[1]
2. **100,000 babies**
   ANGUSTA® has helped more than 100,000 women to give birth.[2]
3. **Ready-to-use dose**
   Angusta® is prepacked in double-layer aluminium foil blisters.[3]
4. **ANGUSTA's® safety profile**
   The safety profile of ANGUSTA® was verified in a compassionate use program.[3]
5. **Nature's helping hand**
   Oral administration allows the pregnant woman the freedom to move around. Walking during labour's first stage reduces labour duration and the risk of caesarean birth.[4]

1. Mundle S et al. Lancet. 2017;390(10095):669-680.
2. Based on sales statistics.
3. Angusta® SmPC.
4. Lawrence A et al. Cochrane Database Syst Rev. 2013 Oct 9;(10):CD003934.

ANGUSTA (misoprostol)

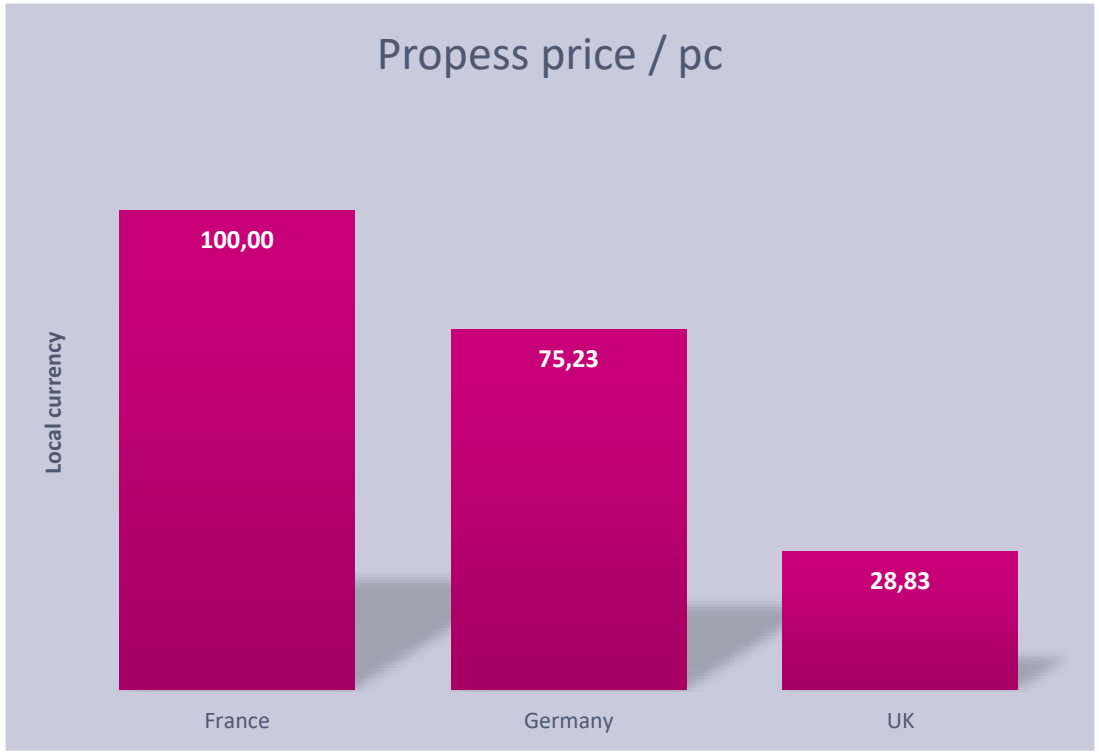
Competitors overview / PROPESS quarterly sales performance



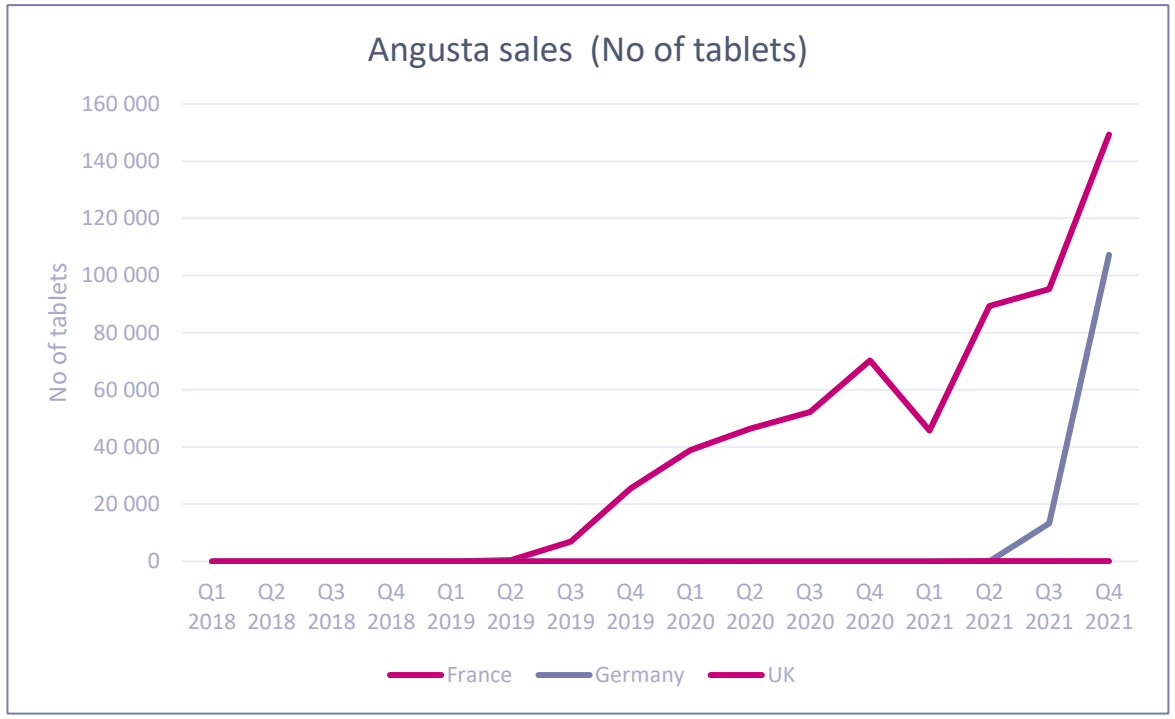


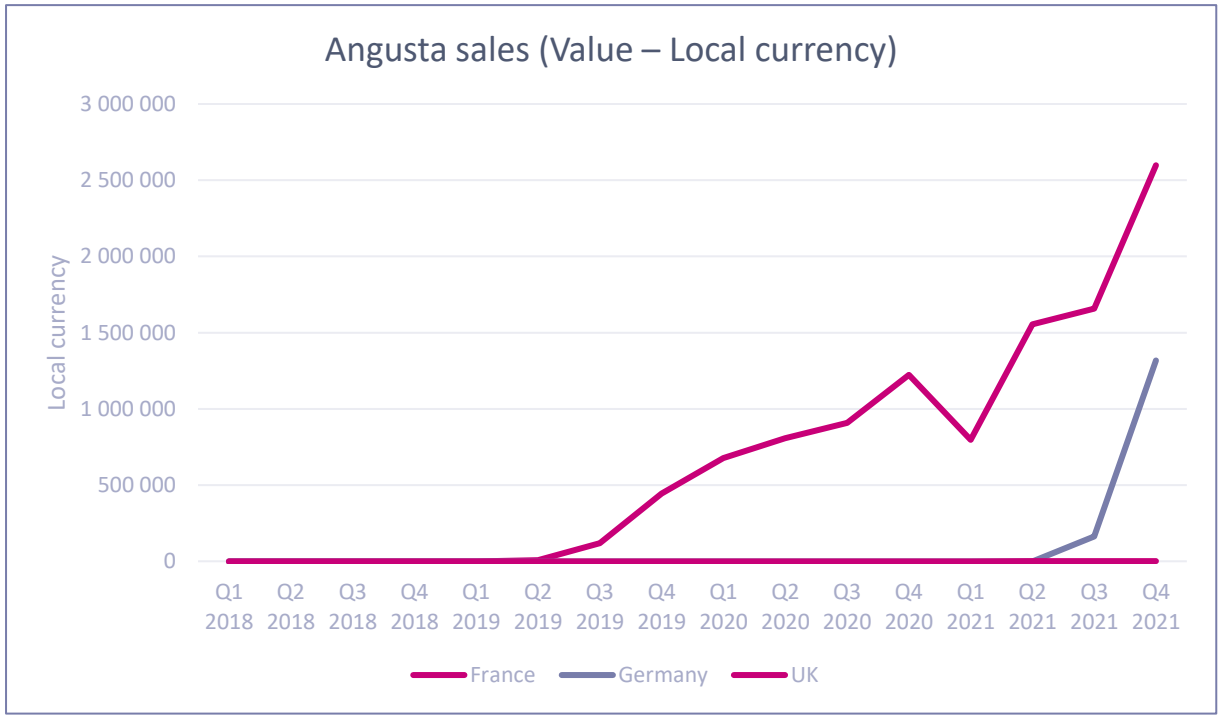
PROPESS		Q1 2018	Q2 2018	Q3 2018	Q4 2018	Q1 2019	Q2 2019	Q3 2019	Q4 2019	Q1 2020	Q2 2020	Q3 2020	Q4 2020	Q1 2021	Q2 2021	Q3 2021	Q4 2021
Volume	France	21 415	25 201	27 471	28 089	22 344	28 331	29 720	28 622	22 312	22 867	26 558	23 511	18 678	19 705	23 720	23 933
	Germany	4 205	4 164	5 919	5 069	5 179	6 649	7 242	7 976	9 264	7 724	8 854	9 130	8 848	10 559	10 024	10 245
	UK	36 330	36 306	38 590	38 581	34 335	36 407	38 714	37 873	35 357	33 616	35 572	34 708	29 706	32 258	34 805	34 445
Value	France	2 141 491	2 520 036	2 747 054	2 808 879	2 234 362	2 833 124	2 971 894	2 862 190	2 231 178	2 286 727	2 655 740	2 351 150	1 867 815	1 970 453	2 372 065	2 393 271
	Germany	316 348	313 268	445 290	381 343	389 620	500 210	544 822	600 040	696 930	581 077	666 086	686 858	665 642	794 361	754 115	770 739
	UK	1 047 394	1 046 335	1 111 978	1 111 944	989 694	1 049 404	1 115 368	1 090 695	1 018 430	968 493	1 025 061	999 900	855 672	929 295	1 002 948	992 532

Competitors overview / PROPESS pricing



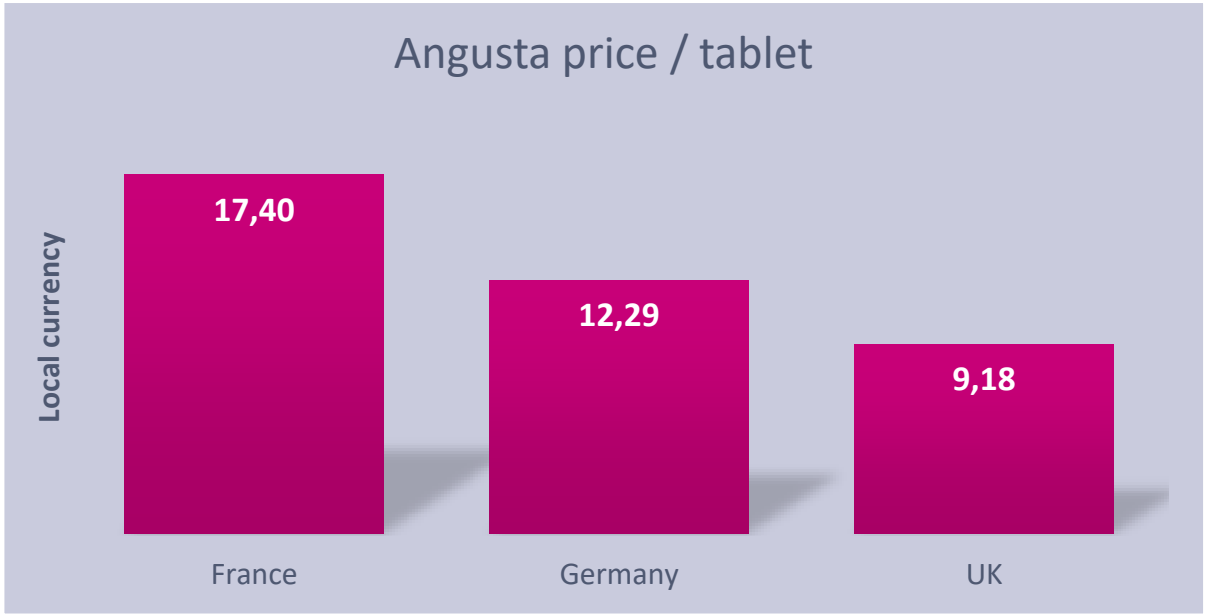
Competitors overview / ANGUSTA quarterly sales performance





ANGUSTA		Q1 2018	Q2 2018	Q3 2018	Q4 2018	Q1 2019	Q2 2019	Q3 2019	Q4 2019	Q1 2020	Q2 2020	Q3 2020	Q4 2020	Q1 2021	Q2 2021	Q3 2021	Q4 2021
Volume	France	0	0	0	0	0	426	6 837	25 509	38 959	46 406	52 204	70 225	45 749	89 297	95 215	149 328
	Germany	0	0	0	0	0	0	0	0	0	0	0	0	0	0	13 222	107 168
	UK	0	0	0	0	0	0	0	0	0	0	0	0	0	80	80	104
Value	France	0	0	0	0	0	7 407	118 981	443 862	677 880	807 460	908 344	1 221 920	796 037	1 553 781	1 656 741	2 598 299
	Germany	0	0	0	0	0	0	0	0	0	0	0	0	0	0	162 469	1 316 836
	UK	0	0	0	0	0	0	0	0	0	0	0	0	0	741	727	955

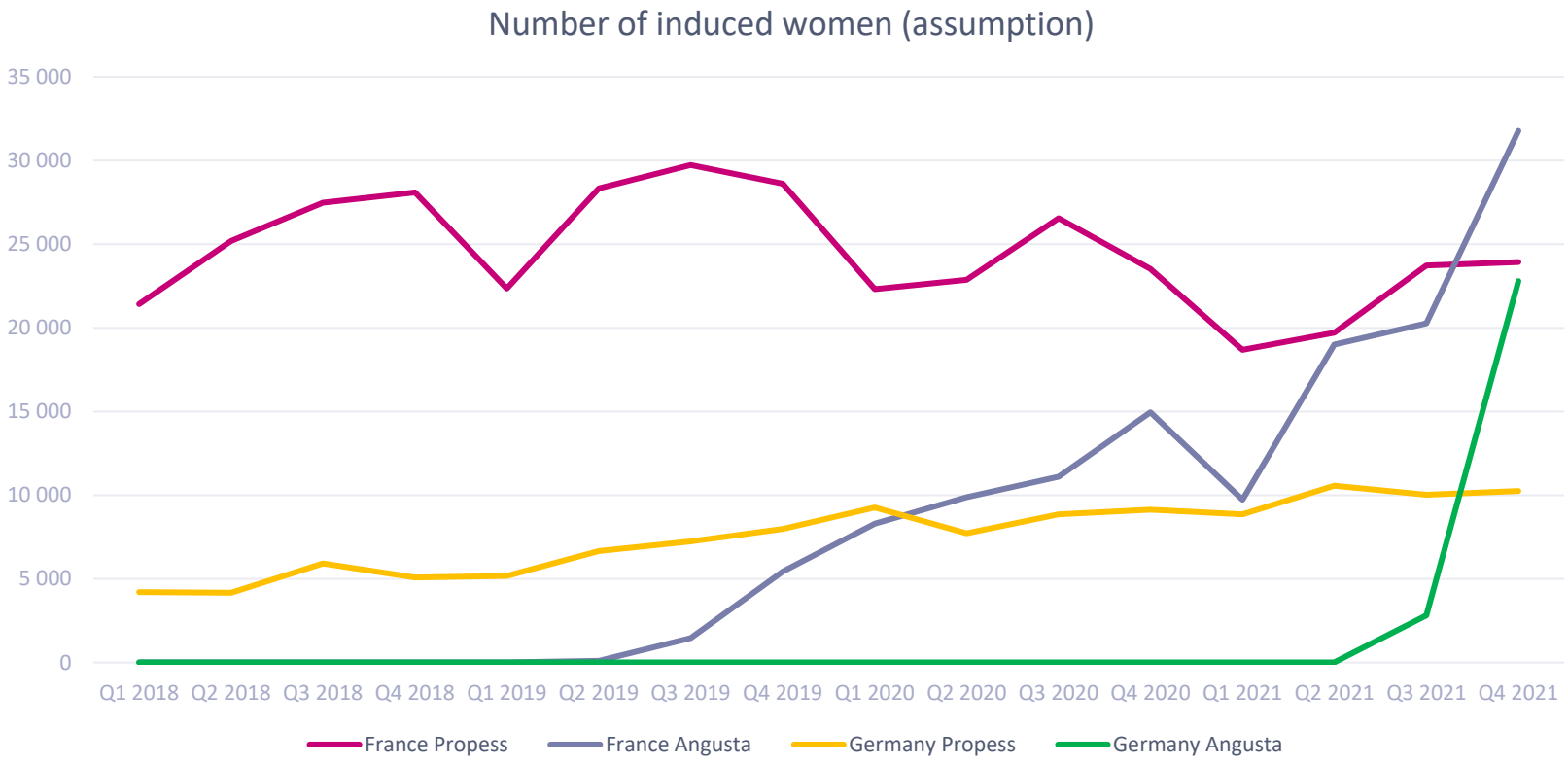
Competitors overview / ANGUSTA pricing



- One 25mcg tablet price varries from 9,2GBP / approx 11€ (UK) - 17.40€ (France)
- Box of 8 tablets costs 88 – 140 €
- In COMRED trial, 4,7 tablets were used / 1 IOL

  = assumed price / IOL procedure is approx. 52 € (UK) – 81€ (FR)

Competitors overview / ANGUSTA performance - Number of induced women / Q



HCPs / UK market analysis / 2021 survey outcomes

- 25% of IOLs managed by mechanical methods
  - Primarilly as out-pts solution and/or for VBACs
  - Pharma preference – habit + mechanical needs training and skills
- Competitors position as stated by HCPs to be used:
  - Propess 81%
  - COOK 50% + Foley 35%
  - Angusta 4%
  - DS 19%
- Frontline treatment: 74% of Propess users positioned Propess as 1st choice (other products had +/- 20%)

- Prioritized efficacy outcome: Vaginal delivery rate / Vag del rate wth 24hrs: 64% vs 26%

- Out-pts ripening: 40% offers routinely, 21% occasionally, 12% implemeting in short term

- 5Ys trends: growing IOL rate, growing rate of high risk pts, growing share of mechanical

HCPs / UK DILAPAN-S perception / 2021 survey outcomes

- **Awareness rate: 29% HCPs**
- DS users
  - 50% extremely satisf + satisf (IOL and TOP users, p 18, N=16) / 58% in IOL (p 39, N=12)
    - however this is a little bit lower than dino - valid for all mechanicals (could it be related to their use in VBACs (more challenging subgroup od IOLs..??)
  - **Only 30% use DS as 1st or 2nd option** (vs Propess – 70% 1st option)
- First impressions: 87% positive
  - Efficacy and safety as key attributes, on third position perception of ease of administration
  - 62% extremelly + very appealing
  - CAVE!: First impression incl non-users is higher than following satisfaction of users !!!
- 57% would be likely / extremelly likely to use / purchase
- 48% agree / strongly agree to have DS as frontline option

Target groups

1/ Healthcare professionals

2/ Expectant mothers

- Two basic target groups, which roles in IOL decision making process can varry. Depending on this, communication strategy should be adjusted to local situation and conditions.
- Symbiosis between HCPs and expectant mothers can be observed.
  - HCPs´ knowledge, communication skills and confidence in product handling is crucial for expectant mothers.
  - Emphasis on importance of „maternal choice“ and mothers´ education is growing. Maternal request is more and more relevant for HCPs.

Models:

1/ HCP > Expectant mother (recommendation/support to informed choice decision making)

2/ Expectant mothers > HCP (interest)

3/ Expectant mother > Expectant mother (influence)

4/ HCP > HCP (sharing experiences and skills/best pracitices/patient advocacy)

2022 Goals

- **HCPs**
  - Build long-term loyalty of current DS users.
  - Manage risks related to loss of confidence due to factors such as incorrect product handling or midwives rotation.
  - Optimise DILAPAN-S users to reach an average share 50%.
  - Attract selected non-users and remove barriers for DILAPAN-S adoption.

- **Expectant mothers**
  - Initiate systematic education to increase awareness and to be preferred option by mothers

HCPs / Segmentation and targeting

	Segment	Comments
1	DS users optimised	DILAPAN-S usage over 50% of IOLs, usualy in frontline. Satisfied with the product, no significant challenges,….
2	DS users un-optimised	Use DILAPAN-S in minor indication(s). And/or facing challenges with outcomes, staff resistance,…
3	Non users	Selection criteria for targeting could be interest in DS, size (No of IOL procedures), part of targeted NHS trust, distance, …

Main barries to adopt DILAPAN-S

1. Long-term habit in PGEs´use, accompanied by quite good satisfaction level
2. Need of training and skills to overcome learning curve
3. Uncertainly with insertion into the cervix (speculum use)
4. Pending perception that PGEs are more effective and mechanicals could raise a risk of infection

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However, there is an increasing appetite for usage of mechanical products, especially with future trends indicating a rise in high-risk pregnancies as well as an increase in outpatient treatment.

Unmet needs

Unmet need	% of respondents
Minimize IOL procedure time	60%
Shorten ripening period	54%
Solution for VBAC	60%
Higher cervical ripening success rate	52%
Universal product	44%
More flexibility	42%
More predictable product	29%
Better safety	21%

Key unmet needs are related to heath care system setting rather than directly to product(s).

Key factors to overcome barriers and to adopt DILAPAN-S

1. Robust clinical data
2. Education
3. Training and support
4. Clinical guideline recommendation
5. Peer to peer sharing experience

DILAPAN-S communication style / HCPs

Build communication style on facts

- Outcomes of clinical trials
- Pear to pear experiences sharing
- Best practices

How to position DILAPAN-S

- DILAPAN-S offers not only product´s related benefit, but also benefits to improve health care system setting.

- DILAPAN-S is a suitable candidate for FRONTLINE use

  DILAPAN-S cervical ripening does not require special staff care. It will allow scheduling and staff time resources will be available for other patients with different needs.

  To adopt DILAPAN-S, cervical ripening effectiveness will remain at least similar as with your current ripener,

  while the issue of PGE´s uterine tachysystoles will be solved and

  induced mothers will be satisfied with gentle ripening.

- It is an universal product suitable for almost all induced women, incl. those indicated for out-pts ripening.

Key components to communicate

Component	Racionale
NICE GL recommendation	HCPs follow GL and this is totally fresh and BIG NEWS
Schedulling / time savings	HCPs are overloaded and key unmet needs are related to time savings
Efficacy	RCTs have provided excelent efficacy outcomes confirming that the product is (at least) comparable to PGEs.
	Company has to offer a support to optimize DS clinical outcomes during learning curve.
Safety	DS offers to solve the issue of PGEs´ frequent uterine tachysystole.
	DS decreases a need of opioids analgetics during IOL procedure.
	Safety profile offers HCPs´ time savings.
Universal product	A wish to have an universal product was listed between unmet needs and DILAPAN-S represents one of the most universal product.
Maternal satisfaction	DILAPAN-S is superior to all key competitors in this parameter.
	NICE GL emphasize role of mother in decision making process.
Non-pharmacological	Majority of DILAPAN-S benefits result from this basic fact.

TOP 5 reasons to choose DILAPAN-S

Recommended by NICE guideline.

1/ Schedulling and time saving

2/ Efficacy

3/ Maternal and neonatal safety

4/ Maternal satisfaction

5/ Versatility

TOP 5 reasons to choose DILAPAN-S

Recommended by NICE guideline.

1	Racionale
Schedulling and time saving	**Non-pharmacological** mode of action brings predictability to ripening process.
	Predictability can improve schedulling of daily work at maternity unit and overal maternal care.
	No special care during cervical ripening / CTG, vaginal exam.
	Minimal number of induced women interupt ripening process due to unexpected complications.
	Staff time and recources are made available for other patients with different need.

TOP 5 reasons to choose DILAPAN-S

2	Racionale
Efficacy	1st round successful cervical ripening is around 80%. 10% higher than PROPESS.
	Vaginal delivery rate up to 80% (depending on clinical protokol and „type of induced women – multips even higher, nullips lower,..). Comparable to PGEs.
	Vaginal delivery within 24 hours comparable to PGE.

3	Racionale
Maternal and neonatal safety	DS offers to solve the issue of PGEs´ frequent uterine tachysystole, incl. those with NRFHT.
	Minimal risk of complication during cervical ripening.
	No serious newborn side effects.
	Decrease need of analgetics (as total rate as strong opioids) during cervical ripening.

TOP 5 reasons to choose DILAPAN-S

4	Racionale
Maternal satisfaction	Superior to PGEs and balloons.
	Lower pain during cervical ripening vs both, Foley and PGEs.
	Lower rate of uterine contractions during cervical ripening vs PGEs.
	Increase possibility to mobilize, relax, sleep.
	NICE GL emphasize role of mother in decision making process.

5	Racionale
Versatility	Broad utility for most types of induced women.
	Only one contraindications, minimal warnings.
	Out-patient ripening.
	Intrauterine growth restriction and reduced fetal movement can benefit from minimal risk of uterine hyperstimulation.
	Solution for VBAC with approx. 50% of vaginal delivery.

Abbreviations used in the presentation

HCP	*Healthcare professional*
IOL	*Induction of labour / labor*
CR	*Cervical ripening*
DS	*Dilapan-S*
DF	*Dilasoft*
RCT	*randomised clinical trial*