

Public Assessment Report

Scientific discussion

**Angusta
(Misoprostol)**

DK/H/2584/001/DC

Date: 09-03-2017

This module reflects the scientific discussion for the approval of Angusta. The procedure was finalised on February 15th 2017. For information on changes after this date, please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Angusta tablets 25 µg, from Azanta Danmark A/S.

The product is indicated for induction of labour.

A comprehensive description of the indications and posology is given in the SmPC.

Misoprostol is a synthetic analogue of Prostaglandin E1 (PGE1), a naturally occurring oxytocic compound. Prostaglandins of the F and E series have been shown to increase collagenase activity in rabbit uterine cervix fibroblasts in vitro and to cause cervical ripening and uterine contraction in vivo. These pharmacodynamic effects are considered to be the mechanism of action relevant for the clinical effect of Angusta.

Various professional societies have recommended induction of labour as a therapeutic option in circumstances where the benefits of expeditious delivery outweigh the risks of continuing the pregnancy. These circumstances generally include full term pregnancy, prelabour rupture of amniotic membranes, hypertensive disorders, maternal medical complications, foetal death, foetal growth restriction, chorioamnionitis, multiple pregnancies, vaginal bleeding and other complications. Various methods for labour induction are applied and include physical/mechanical methods (e.g., membrane sweeping, manual rupture of membranes, extra-amniotic saline infusion) and pharmacologic methods (e.g., i.v. oxytocin and prostaglandins by various routes of administration).

A number of guidelines recommend the use of misoprostol for the induction of labour. These recommendations are based completely or in part on the Cochrane review of misoprostol for the induction of labour although not all on the latest version of the review.

In 2011, the WHO issued 'Recommendations for induction of labour recommending misoprostol administered orally or vaginally for induction of labour'. In addition, a number of countries and professional societies have developed treatment guidelines for the use of misoprostol (oral and other formulations) for induction of labour.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC (full mixed application).

II. QUALITY ASPECTS

II.1 Introduction

Each Angusta tablet contains 25 µg misoprostol as active substance.

The tablet is white, uncoated oval shaped with the dimensions 7.5 x 4.5 mm with a score line on one side and plain on the other.

Angusta is available in a pack of double layer aluminium foil blister containing 8 tablets.

The excipients are: Hypromellose, cellulose, microcrystalline; maize starch; croscopovidone; croscarmellose sodium and silica, colloidal anhydrous.

Compliance with Good Manufacturing Practice

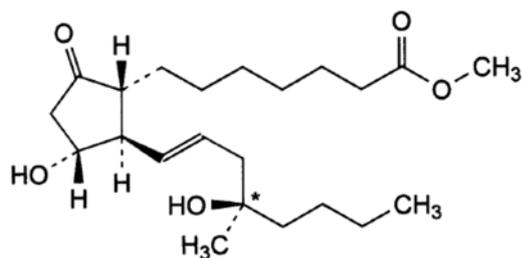
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The drug product contains the active substance misoprostol.

The active substance, misoprostol, is described in the European Pharmacopoeia. It is a clear, colourless or yellowish, oily liquid, hygroscopic. It is practically insoluble in water, soluble in ethanol (96%), sparingly soluble in acetonitrile.

Structural formula:



its epimer at C* and their enantiomers

Misoprostol has four chiral centres. The centre at C16 is racemic and the centres at C8, C11 and C12 are controlled relative to each other with cis substitution on the cyclopentanone ring. Misoprostol is therefore a mixture of four stereo isomers.

The CEP procedure is used for the active substance.

Based on presented stability studies, an appropriate re-test period has been set.

II.3 Medicinal Product

The development of the product has been described, the choice and function of excipients have been satisfactorily explained and the manufacturing method has been discussed.

To stabilise the active substance an intermediate of 1% misoprostol in hypromellose is manufactured, which can be stored during a holding period (8 weeks). The manufacture and control of the intermediate is adequately described, and process validation demonstrated homogeneity of the 1% misoprostol dispersion intermediate.

Having the low content of active substance in the finished product, the manufacturing methods are critical and homogeneity is addressed in the process validation of the dispersion and tablet blend. Due to the low content of API the formulation is considered a specialised pharmaceutical form and the manufacture is a non-standard method. The proposed batch size is supported by process validation data of three batches.

The finished product specifications are adequately drawn up and justified. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches from the manufacturing site. The batch analysis results show that the finished product meets the specifications consistently.

The conditions used in the stability studies are according to the ICH stability guideline. Currently only stability results of up to 9 months are reported on three commercial scale batches. The start of shelf-life is calculated from the inclusion of the 1% misoprostol dispersion. The proposed shelf-life (1 year) is accepted based on 9 months long term data as stability results are within specification at intermediate conditions but OOS results are observed at accelerated conditions. Storage conditions: Store in the original package in order to protect from moisture.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The active substance and the finished product have been adequately described.

From a quality point of view, the benefit/risk ratio of the product is considered positive.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Non-clinical investigations are normally not required when there is sufficient well-documented clinical experience to establish all aspects of clinical efficacy and safety. Therefore, the lack of new non-clinical pharmacodynamic, pharmacokinetic or toxicological studies is considered acceptable.

The non-clinical overview is based solely on bibliographical research including 15 references dated from 1985 to 2011.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Pharmacology

The primary pharmacodynamic properties for misoprostol as well as safety pharmacology are considered sufficiently addressed and no further non-clinical studies are required.

III.3 Pharmacokinetics

Non-clinical pharmacokinetics of misoprostol were described with reference to one published article (review by Schoenhard et al., 1985). In spite of the sparse data on misoprostol exposure of misoprostol acid, the total exposure of drug related material is given. Comparison of IV and oral administration suggest a high first pass metabolism, but with a total exposure that ensure that the high dose group of the safety studies (dog: 300 µg/kg/day, rat: 9000 µg/kg/day) exceeds the human exposure (25-50 µg every 2-4 hours) of both the pharmacologically active metabolite and other major metabolites.

III.4 Toxicology

Only few and relatively old (1980s) articles were cited to describe the toxicology of misoprostol. The acute and repeat-use toxicology studies cited in the non-clinical overview derive from one single article (Kotsonis et al., 1985). This article was published in *Digestive Diseases and Sciences* and the studies focus on gastrointestinal effects of misoprostol, and not so much toxicology findings in other major organ systems. Experimental detail is brief and original references are only cited occasionally. However, the toxicology profile of misoprostol is considered well known and safety margins are considered sufficient for the proposed indication and administration posology of misoprostol in this application. Human safety data supersede the need for further non-clinical toxicology studies and no carcinogenic potential of misoprostol was found in rats or mice.

According to the guideline on 'Non-clinical documentation for mixed marketing authorisation applications' (CPMP/SWP/799/95), investigations of embryo-fetal toxicity and peri/post-natal development are not necessary if sufficient data from exposures in pregnant women and neonates are available. However, for the proposed indication, no safety concerns are identified in the non-clinical studies cited and no further non-clinical studies are thus required. Emphasis is on clinical data and relevant information regarding pregnancy is described accordingly in the SmPC section 4.6 and 5.3.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Misoprostol PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. No further studies are deemed necessary.

III.6 Discussion on the non-clinical aspects

From a non-clinical point of view, the benefit/risk ratio of the product is considered positive.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview is primarily based on the Cochrane review of ‘Oral misoprostol for induction of labour’ including 76 trials comprising a total of 14,412 women.

In addition, a recently conducted pK and comparative bioavailability trial comparing Cytotec and Angusta provides bridging to the extensive literature base on the off-label use of Cytotec for induction of labour.

IV.2 Pharmacokinetics

In order to bridge the data presented in the Cochrane review (2014) on the use of oral misoprostol for the induction of labour, the Applicant has conducted a PK-PD study.

The study is a two centre, single dose, open-label, randomised, parallel design, study of two misoprostol formulations (Angusta 25 µg tablets vs. Cytotec 200 µg tablets (as a fraction (equal to 25 or 50µg) of a dissolved/dispersed Cytotec tablet), following single oral administration (to induction of labour in pregnant women) and comparison of safety of the two formulations following repeat dosing until labour. PK comparison:

Subjects were assigned to the treatment groups sequentially, i.e. treatment group A was completed before treatment group B was open for enrolment.

Angusta misoprostol tablets, 25 µg was administered as whole unbroken tablets

- oral administration, 25 µg 2-hourly (Cohort A) or

- oral administration, 50 µg 4-hourly (Cohort B)

Cytotec 200 µg misoprostol tablets (marketed product in SE), dissolved in 100 mL water. 12.5 or 25 mL was dispensed to the subjects according to treatment cohort

- oral administration, 25 µg (12.5 mL) 2-hourly (Cohort A) or

- oral administration, 50 µg (25 mL) 4-hourly (Cohort B)

Results:

25µg dose comparison: AUC_{0-t} (Ratio: 71.0%, CI: 51.2-98.5) C_{max} (Ratio: 66.3%, CI: 43.8-100.3)

50µg dose comparison: AUC_{0-t} (Ratio: 105.2%, CI: 75.5-150.7) C_{max} (Ratio 104.0%, CI: 70.9-152.5)

New PK data for the Group A (25µg dose) Angusta group was presented during the procedure, since one Subject (L06) should not be excluded as dosing is documented (although no measurable values were observed in PK profile for this subject). Change in calculations influence PK data, but not CI (confidence intervals) as value 0.00pg/ml is used for each sampling point.

	Angusta 25 µg n=11	Cytotec 25 µg n=12	Angusta 50 µg n=12	Cytotec 50 µg n=12
C_{max} (pg/mL)	26.64 (22.48)	37.58 (13.53)	57.87 (41.28)	53.97 (23.79)
t_{max} (hours)	0.47 (0.54)	0.27 (0.24)	0.46 (0.42)	0.23 (0.14)
AUC _(0-∞) (h ⁺ pg/mL)	18.22 (10.69)	26.30 (9.90)	53.79 (20.95)	55.02 (28.80)
AUC (h ⁺ pg/mL)	26.78 (15.43)	35.61 (13.18)	64.05 (22.80)	66.63 (33.22)
$t_{1/2}$ (hours)	0.82 (0.58)	0.76 (0.47)	0.74 (0.51)	1.05 (0.86)
V_z/f (mL/kg)	11329 (6170)	9680 (5132)	10913 (6346)	14866 (9769)
CL/f (mL/h/kg)	11659 (6316)	9682 (2786)	11419 (5264)	12054 (5851)

Cross-reference: Appendix 16.1.9

Study	Product	Dose (µg)	N	AUC (h·pg/ml)	AUC _{Norm} ¹ (h·pg/ml)	V_z/f (l/kg)	$t_{1/2}$ (h)
Present	Angusta	25	10/11	26.78±15.43 (N=11) ²⁾	107.8±61.72 (N=11) ²⁾	11.33±6.17 (N=10) ³⁾	0.82±0.58 (N=10) ³⁾
Present	Cytotec	25	12	35.61±13.18	142.4±52.72	9.68±5.13	0.76±0.47
Present	Angusta	50	12	64.05±22.80	128.1±45.60	10.91±6.35	0.74±0.51
Present	Cytotec	50	12	66.63±33.22	133.3±66.44	14.87±9.77	1.05±0.86
Foote et al.	Misoprostol	Oral 400	24	421.4±263.1	105.4±65.78	13.6±8.0	0.70±0.72

SL: Sublingual

1) Normalized to a dose of 100 µg

2) L04 is missing due to a terminal slope not being assessable.

3) L04 and L06 are missing due to a terminal slope not being assessable.

Cross-reference: Appendix 16.1.9

Robust data, in order to show equivalence in PK data (for a limited number of women during labour induction, for either Group A (25µg dosing group) or Group B (50µg dosing group) according to pre-study established acceptance criteria (criteria in line with EU BE Guideline general acceptance criteria), have not been presented. Study outcome (from study with purpose to investigate PK and mimicking real life clinical conditions) may however offer some reassurance that Cytotec and Angusta have similar PD.

There may be numerous reasons why study has not produced robust results, from which any conclusion on equivalence could be made.

Very few subjects have been included in each dosing group (sample size was chosen arbitrarily) in a parallel study design where influence of non-standardized conditions was not considered in sample size decision.

The observed test/reference Ratios are different in Group A and Group B (only about 70% in Group A). The Group A Ratio may have been influenced by the applied 2h dosing frequency. Less than 80% of AUC (profile) is obtained in 16 of 24 Group A subjects. The $T_{1/2}$ observed is longer than expected which influence amount of profile covered. With expected $T_{1/2}$ about 3x $T_{1/2}$ could have been covered. The analytical method sensitivity may also have had a greater influence on Group A results.

The results presented from the study are based on very variable conditions and very wide confidence intervals inevitably result from such study design and conditions. Results cannot in any way be considered robust or indicate equivalence. Results can only be used as a very rough comparison of systemic exposure following administration of Angusta and Cytotec (as solution/dispersion of tablet).

IV.3 Pharmacodynamics

Misoprostol is a synthetic analogue of Prostaglandin E1 (PGE1).

Prostaglandins are capable of inducing production of hyaluronic acid by cervical fibroblasts, causing increased hydration and alteration of the composition of glycosaminoglycan and proteoglycan. Prostaglandins may act as chemotactic agents, promoting the infiltration of leukocytes and macrophages

into the cervical stroma. These inflammatory cells could be the source of the specific degradative enzymes that cause the changes in the extracellular matrix that are associated with ripening of the cervix. Prostaglandins have potent uterotonic activity caused by their effect of increasing intracellular calcium and activating myosin light-chain kinase, leading in turn to actin and myosin undergoing conformational changes that enable them to slide over each other, causing shortening of the muscle cells and inducing uterine contractions.

The effect of misoprostol on the rest of the human body has been described. The plasma concentrations known to have an effect (i.e. cause uterine contraction) have been sufficiently compared to the plasma concentrations measured in the PK-PD study. Pharmacodynamic interactions have been sufficiently discussed.

IV.4 Clinical efficacy

Various professional societies have recommended induction of labour as a therapeutic option in circumstances where the benefits of expeditious delivery outweigh the risks of continuing the pregnancy. These circumstances generally include full term pregnancy, prelabour rupture of amniotic membranes, hypertensive disorders, maternal medical complications, foetal death, foetal growth restriction, chorioamnionitis, multiple pregnancies, vaginal bleeding and other complications. Various methods for labour induction are applied and include physical/mechanical methods (e.g., membrane sweeping, manual rupture of membranes, extra-amniotic saline infusion) and pharmacologic methods (e.g., i.v. oxytocin and prostaglandins by various routes of administration).

A number of guidelines recommend the use of misoprostol for the induction of labour. These recommendations are based completely or in part on the Cochrane review misoprostol for the induction of labour although not all on the latest version of the review.

In 2011, the WHO issued 'Recommendations for induction of labour recommending misoprostol administered orally or vaginally for induction of labour'. In addition, a number of countries and professional societies have developed treatment guidelines for the use of misoprostol (oral and other formulations) for induction of labour e.g. The Danish Council for the Use of Expensive Hospital Medicines (RADS), Danish Society for Obstetrics and Gynaecology (DSOG), Norwegian Society of Obstetrics and Gynecology (NSOG), Swedish Society of Obstetrics and Gynecology (SFOG) and American College of Obstetricians and Gynecologists (ACOG).

Angusta (misoprostol 25 µg tablet)

Angusta, tablet 25 µg is a new proprietary formulation of misoprostol for induction of labour. Azanta proposes the following indication for Angusta: Induction of labour. Dosage: 25 µg orally every 2 hours or 50 µg orally every 4 hours. Maximum dose is 200 µg over 24 hours. It is recommended that Angusta is administered by trained obstetric personnel. Angusta is contraindicated for induction of labour in women with previous caesarean section or other major uterine surgery.

The efficacy of Angusta (oral misoprostol) is based on the Cochrane review (2014) of 'Oral misoprostol for induction of labour' which included 76 trials comprising a total of 14,412 women. Objectives of the review were to determine, from randomised controlled trials, the effectiveness and safety of oral misoprostol for third trimester induction of labour. The review included only trials with some form of random allocation to treatment groups and that reported at least one of five pre-specified outcomes: vaginal delivery not achieved within 24 hours (includes all caesarean sections), uterine hyperstimulation with foetal heart rate (FHR) changes, caesarean section, serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood) and serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit, septicemia). A PK-PD study comparing Angusta to Cytotec has been conducted by the Applicant to bridge the data from the Cochrane review. The studies in the Cochrane review all seem to have been conducted with Cytotec although it is not entirely clear whether tablets or parts of Cytotec tablets were used or if an oral solution of Cytotec has been used in the clinical studies. With regard to the three pivotal studies, two were conducted with misoprostol oral solutions while one was conducted with misoprostol oral capsules. The PK-PD study should not be viewed as a strict bioequivalence study as it has not been performed under conditions usually required to demonstrate bioequivalence. Although it does seem that exposure (AUC) and the efficacy of Angusta 50 µg/4 hours and Cytotec 50 µg/4 hours are similar. However, the exposure of Angusta 25 µg/2 hours is approximately 30% less than 25 µg/2 hours Cytotec although the efficacy appear to be slightly better with Angusta 25µg/2 hours. The PK/PD study has several deficiencies that makes firm conclusion difficult with regards to PK. The PD outcomes offer some

reassurance that Cytotec and Angusta have similar PD properties. To further bridge the Angusta formulation to the Cytotec formulation, the Applicant has shown that from a quality point of view using dissolution data the bioavailability of Angusta 25 µg tablet after oral administration is expected to be comparable to Cytotec tablets 0.1 mg and 0.2 mg. The excipients are not expected to affect absorption.

29,000 women have been treated for the induction of labour in Denmark, Norway and Finland with Angusta in a compassionate use program. Unfortunately, no efficacy data are available from this program.

There is little doubt that oral misoprostol is used for induction of labour.

The Cochrane review shows that oral misoprostol is effective in inducing labour e.g. oral misoprostol vs. placebo: Likelihood of giving birth vaginally within 24 hours risk ratio (RR) 0.16, 95% confidence interval (CI) 0.05 to 0.49). Caesarean section (CS) rates, RR 0.72, 95% CI 0.54 to 0.95).

The efficacy is comparable to other medicines approved for the induction of labour, e.g. oral misoprostol versus vaginal dinoprostone: cesarean section rate 21% versus 26%; RR 0.88, 95% CI 0.78 to 0.99). Women not achieving vaginal birth within 24 hours, RR 1.09, 95% CI 0.99 to 1.20; Oral misoprostol versus i.v. oxytocin: cesarean section rate, RR 0.77, 95% CI 0.60 to 0.98.

However, the conclusion of the Cochrane review cannot readily be extrapolated to the applied medicinal product, Angusta, 25 µg with the proposed posology 25 µg/2 hours or 50 µg/4 hours. The conclusions in the Cochrane review are based on meta-analysis of studies using different dosing regimens. In order to assess the benefit-risk of the proposed posology, 25 µg/2 hours or 50 µg/4 hours, an analysis and discussion of studies conducted with this dosing regimen was requested.

The two studies comparing 20 µg/hours misoprostol to dinoprostone show no difference in effect and the largest study with the best design show no difference with regards to complications following the use of misoprostole (hyperstimulation). This means that compared to a licensed medicine product with an indication of induction of labour, oral misoprostol 20 µg/2 hours has similar efficacy and safety. However, of the studies with a posology of either 20 µg/2 hours or 25 µg/2 hours only the Dood 2006 study (20 µg/2 hours) is considered a truly pivotal study as it has an adequate design (double blinded etc.) and is sufficiently large. Extrapolation from this study to support the 25 µg/2 hours Angusta posology is provided from the open label study Aalami-Harandi 2013 where 25 µg/2 hours were used. This study supports that the dose is safe. The extrapolation is further supported by PK simulation data.

PROM

The Applicant has applied for the indication use in the induction of labour. It is important to distinguish between two different clinical presentations. In women with premature rupture of membranes (PROM) it can be said that the natural cause of labour has commenced and that the administration of misoprostol would thus further assist faster delivery. This also means that the safety and efficacy in this population is likely to differ from a situation where natural labour has not commenced. There is some evidence that prolonged labour after rupture of membranes increases the risk of especially maternal infections and perhaps neonatal infection. Thus, there is a clinically relevant benefit in decreasing the time to delivery. Compared to placebo there is little doubt that vaginal delivery is achieved faster with 50µg/4 hours oral misoprostol than with placebo in women with PROM. This is clinically relevant as decreased time to delivery is likely to reduce the risk of infection.

Two double blind studies Levy 2007 (n=64 misoprostol, n=66 placebo) and Cheung 2006 (n=33 misoprostol, n=32 placebo) show that vaginal delivery is achieved faster with oral misoprostol 50 µg/ 4 hours than with placebo, but with a small risk of hyper-stimulation which was, however only found in one study. There was no difference with regards to the frequency of cesarean sections. The open-label study Rath 2007 (n=150 misoprostol, n=150 placebo) support these results and does not find a difference with regards to tachystole. All studies included only women with PROM. There was a time difference between placebo and misoprostol in time from PROM to delivery of 6.6 to 11 hours. The safety and efficacy of 50 µg/4 hours oral misoprostol in women with PROM is further supported by the open-label study Butt 1999 comparing oral misoprostol to oxytocin (n=55 in the misoprostol arm, n=53 in the oxytocin arm). In this study, vaginal delivery was achieved approximately 3.5 hours faster with oxytocin than with misoprostol with similar safety. Oxytocin is in clinical practice used in women with PROM in Denmark. Additional support of the safety of 50 µg/4 hours in women with PROM from two additional open label studies and double blind studies with 100 µg oral misoprostol confirm that 50 µg/4 hours is the preferred dose compared to 100 µg. The number of women with PROM exposed in proposed

indication to 363 and overall 1050 women with PROM are exposed to oral misoprostol. Thus a sufficiently large number of women with PROM have been exposed to 50 µg/4 hours and other doses of misoprostol (primarily larger doses) to assess the safety profile.

Only one study in women with PROM have used the posology 20 µg/2 hours. In this study the cervix was not ripe. National and international guidelines state that the choice of treatment for induction of labour depends on the ripeness of the cervix. Thus, extrapolation from other studies using the posology 20-25 µg/2 hours can be extrapolated to women with PROM with an unripe cervix.

Other indications

Other clinical situations where induction of labour is warranted could be preeclampsia, hypertension, gravitas prolongation etc. Here the idea of administering misoprostol (or other prostaglandins) is to promote cervical ripening as the first step in labour induction of women with unfavourable cervixes. This alone initiates labour in many women, and obviates the need for oxytocin in these patients.

In support of this clinical situation, the primary evidence is provided from studies where 50 µg/4 hours oral misoprostol has been compared to 50 µg vaginal misoprostol in three double blind studies, Bennett 1998 (n=104 oral misoprostol, n=102 vaginal misoprostol), Mehrota 2010 (n=60 oral misoprostol, n=68 vaginal misoprostol) and Jindal 2011 (n=51 oral misoprostol, n=52 vaginal misoprostol).

Studies comparing 50 µg oral misoprostol to a lower dose of vaginal misoprostol does not directly support the double blind studies comparing 50 µg oral misoprostol to 50 µg vaginal misoprostol, but does provide valuable safety data.

The vaginal misoprostol used in the studies do not appear to be licensed product for the indication of labour. Vaginal administration of 25 µg/2-4 hours or 6 hours vaginally appear to be a well-established clinical practice. Data from studies comparing 50 µg/4 hours oral misoprostol indicate that oral misoprostol is as effective and safe as 25 µg vaginal misoprostol. It does seem that higher doses (100 µg and 200 µg) is associated with a higher risk of hyper-stimulation. Thus, 25 µg/2 hours and 50 µg/4 hours seem to be a more appropriate dosing regimen than 100 µg/4-6 hours or 200 µg.

IV.5 Clinical safety

The overall safety database appears to be adequate. More than 14,000 women have been exposed in the Cochrane review on oral misoprostol for the induction of labour. 128 women have been exposed to the dose 25 µg/ hours which is considered insufficient. 2515 women have been exposed to 50 µg/ 4hours oral misoprosrol.

Supportive safety data are derived from the PK-PD study comparing Angusta to Cytotec. This show similar safety across treatment groups. Further, spontaneous adverse event reports are available from the 29,000 women who have been exposed to Angusta in the compassionate use program. These show overall, that the reported adverse events resemble the observed adverse events in the clinical studies included in the Cochrane review.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Angusta.

The agreed summary list of safety concerns with no additional pharmacovigilance measures is as follows:

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> ▪ Uterine hyperstimulation ▪ Foetal heart rate disorder due to uterine hyperstimulation ▪ Perinatal asphyxia due to uterine hyperstimulation ▪ Uterine rupture
Important potential risks	<ul style="list-style-type: none"> ▪ Unintentional overdose by patient*
Missing information	None

*To minimise this risk the pack size is small and restricted to 8 x 25µg tablets.

IV.7 Discussion on the clinical aspects

The Applicant has primarily based the application on the Cochrane review (2014) of 'Oral misoprostol for induction of labour' which included 76 trials comprising a total of 14,412 women. In addition, a PK-PD study comparing Angusta to an oral solution of Cytotec has been conducted by the Applicant to bridge the data from the Cochrane review. Study was conducted in accordance with GCP.

The Cochrane review shows that oral misoprostol is effective in inducing labour e.g. oral misoprostol vs. placebo:

Likelihood of giving birth vaginally within 24 hours risk ratio (RR) 0.16, 95% confidence interval (CI) 0.05 to 0.49). Caesarean section (CS) rates, RR 0.72, 95% CI 0.54 to 0.95).

The efficacy is comparable to other medicines approved for the induction of labour, e.g. oral misoprostol versus vaginal dinoprostone: caesarian section rate (21% versus 26%; RR 0.88, 95% CI 0.78 to 0.99). Women not achieving vaginal birth within 24 hours, RR 1.09, 95% CI 0.99 to 1.20; Oral misoprostol versus i.v. oxytocin: caesarean section rate, RR 0.77, 95% CI 0.60 to 0.98.

These results are based on meta-analysis of studies using differing dosing regimens of oral misoprostol. It is however, imperative that sufficient evidence in support of the proposed posology is presented. This has been done for the 50 µg/4 hours and the 25 µg/2 hours posology.

Compared to placebo there is little doubt that vaginal delivery is achieved faster with 50µg/4 hours oral misoprostol than with placebo in women with PROM. This is clinically relevant as decreased time to delivery is likely to reduce the risk of infection. Studies comparing oral misoprostol 50 µg/4 hours in other indications also show that misoprostol is as effective and safe as the clinical well-established treatment of 25 µg vaginal misoprostol.

The pivotal study, Dodd 2006, shows that misoprostol 20 µg/2 hours is effective and as safe as the already approved medicines dinoprostone for the use in labour induction. Based on PK data and a supportive open label study using 25 µg/2 hours, these results can reasonably be extrapolated to the 25 µg/2 hours dose.

Bridging between Angusta and Cytotec used in the published articles is supported primarily by the PD outcome (time to delivery) from the PK-PD study and also by quality aspects such as a rapid dissolution of both Angusta and Cytotec 0.1 mg and 0.2 mg tablet.

The PK/PD study has several deficiencies that makes firm conclusion difficult with regards to PK. The PD outcomes offer some reassurance that Cytotec and Angusta have similar PD properties.

29,000 women have been treated for the induction of labour in Denmark, Norway and Finland with Angusta in a compassionate use program. Unfortunately, no efficacy data are available from this programme.

Misoprostol used for the induction of labour can cause uterus hyper-stimulation. As a possible consequence of this caesarean section, serious neonatal morbidity or perinatal death, serious maternal morbidity or death, uterine rupture and meconium staining could occur. Spontaneous adverse event reports are available from the 29,000 women who have been exposed to Angusta in the compassionate use program. These show overall, that the reported adverse events resemble the observed adverse events in the clinical studies included in the Cochrane review.

Oral misoprostol is used for the induction of labour. Many national and international guidelines recommend the use of oral misoprostol in doses resembling the proposed posology by the Applicant. Many of these base their recommendation on the Cochrane review on the use of oral misoprostol for the induction of labour, although not all on the latest version of the review.

Oral misoprostol can induce labour and the efficacy is likely dose dependent. However, misoprostol can also cause hyper-stimulation, which may cause serious adverse events for the mother as well as the neonate.

Benefit-risk balance

The induction of vaginal labour should be balanced with the risk of hyper-stimulation. A slow labour might result in a caesarean section or foetal distress but misoprostol may cause hyper-stimulation which could also cause increased risk of foetal distress. This could lead to caesarean section, serious adverse

events of the neonate, low Apgar score etc. It might also lead to uterus rupture. Considering this, it is important to establish which dosing regimen of misoprostol has the best benefit-risk balance.

Discussion on the benefit-risk assessment

Oral misoprostol can be used to induce labour and an overall meta-analysis of a wide range of dosing regimen show that oral misoprostol is more effective than placebo and appear to be as effective as other medicines used/approved for the induction of labour. Regardless of the indication for induction of labour, in women with an unripe cervix the dose of 25 µg/2 hours or 50/4 hours has shown comparable efficacy and safety to already approved medicines or clinically well-established medicines used for the induction of labour.

Conclusions

The overall B/R of Angusta is positive.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Angusta tablets 25µg has a proven chemical-pharmaceutical quality and a favorable efficacy and safety profile.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The MAH presented a risk management plan summarising the safety concerns. There are no additional pharmacovigilance or risk minimisation measures.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that the application for Angusta in the treatment of induction of labour was approvable.

The decentralised procedure was finalised on 15 February 2017. Angusta, tablet 25 µg was authorised in Denmark on 1 March 2017.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs) no European harmonised birth date has been allocated. The next data lock point for misoprostol is 31-05-2017.

The date for the first renewal will be 15 February 2022.

There were no post-approval commitments made during the procedure.