AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Misoprostol (Mysodelle®)
200 microgram vaginal delivery system

Reference number: 3627

RESUBMISSION

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Misoprostol (Mysodelle®) 200 microgram vaginal delivery system

This assessment report is based on evidence submitted by Ferring Pharmaceuticals (UK)[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Misoprostol (Mysodelle®) for the induction of labour in women with an unfavourable cervix, from 36 weeks gestation, in whom induction is clinically indicated[2].
Dosing	Mysodelle® 200 micrograms is a controlled-release formulation that releases misoprostol at a rate of approximately 7 micrograms per hour over a period of 24 hours. The maximum recommended dose is one Mysodelle® vaginal delivery system (200 micrograms). Mysodelle® should only be administered by trained obstetric personnel in a hospital setting where facilities for continuous fetal and uterine monitoring are available. The condition of the cervix should be assessed carefully before Mysodelle® is used. After insertion, uterine activity and fetal condition must be carefully monitored. Please refer to the Summary of Product Characteristics for further information regarding posology and method of administration[2].
Marketing authorisation date	17 October 2013

2.0 DECISION CONTEXT

2.1 Background

The All Wales Medicines Strategy Group (AWMSG) has previously appraised Mysodelle® for the indication under consideration and issued a non-recommendation[3]. The company has provided an updated submission for Mysodelle® that includes a new patient preference survey and a new cost-effectiveness model[1].

In 2015, the total number of live births in Wales was 33,279[4], and 24.9% were inductions in 2014–2015; evidence suggests that the proportion of births requiring induction in Wales is increasing each year[5]. When judging the need for induction of labour, the clinician and the pregnant woman must decide whether the interests of the mother or the baby, or both, will be better served by inducing labour or continuing the pregnancy[6]. Circumstances when induction of labour may be indicated include prevention of prolonged pregnancy and prelabour rupture of membranes[7]. Induction of labour has an impact on birth experience and the health of women and their babies, and so needs to be clinically justified; it may also be less efficient and is usually more painful than spontaneous labour[6]. Epidural analgesia and assisted delivery are more likely to be needed if labour has been induced[6]. Treatment and care must take into account the individual needs and preferences of women, who should have the opportunity to make informed decisions about their care in partnership with their healthcare professionals[7].

National Institute for Health and Care Excellence (NICE) clinical guideline 70 (CG70) states that vaginal prostaglandin E2 (also known as dinoprostone[8]) is usually the preferred method of induction of labour, administered as a gel, tablet or controlled-release pessary[7]. Misoprostol, a synthetic analogue of prostaglandin E1, causes cervical ripening and uterine contraction[2]. In the misoprostol vaginal delivery system (Mysodelle®), misoprostol is released *in vivo* over a period of 24 hours from a polymer insert contained within a retrieval system[2].

2.2 Comparators

The comparator included in the company submission is dinoprostone 10 mg vaginal delivery system (Propess®)[1].

2.3 Guidance and related advice

- NICE pathway. Inducing labour (2017)[9].
- NICE quality standard (QS60). Inducing labour (2014)[6].
- NICE CG70. Inducing labour (2008)[7]. A NICE surveillance report was published in 2017, which states that a partial update is necessary for NICE CG70[10]. An update to the guideline is in development and the expected publication date is yet to be confirmed[11].

AWMSG has previously issued a non-recommendation for the use of Mysodelle® for the indication under consideration[3]. AWMSG was not convinced that the evidence presented was sufficient to demonstrate therapeutic equivalence between Mysodelle® and the comparator. Therefore, the evidence to justify the cost-minimisation analysis (CMA) presented in the submission was insufficient for AWMSG to recommend its use[3].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The submitting company provided evidence from the pivotal EXPEDITE phase III study, which directly compared the efficacy of Mysodelle® versus Propess®[1]. The company submission also included evidence from a new online survey, which explored patient preference for shorter or longer labours, with associated pain intensity patterns[1].

3.1 EXPEDITE study

EXPEDITE was a double-blind, randomised, multicentre study, conducted in the USA in 1,358 pregnant women at term, who were assigned to receive either Mysodelle® or Propess®[1,12]. Patients were of at least 36 weeks and 0 days of gestation, had an unfavourable cervix (baseline modified Bishop score ≤ 4, see Glossary), were aged ≥ 18 years, had parity ≤ 3 and had singleton pregnancies[12]. The most common primary reasons for induction were being post-term (32.2%), hypertension (12.2%) and elective delivery (12.2%)[1,13]. The treatment was placed in the posterior vaginal fornix using water-soluble gel as needed and patients were continually monitored for uterine and fetal heart rate activity[12]. The vaginal delivery system was removed at onset of active labour; at the completion of the 24-hour dosing period; at the occurrence of any intrapartum adverse event; or at maternal request. Oxytocin administration was permitted 30 minutes after removal of the delivery system if the patient was not in active labour and had reassuring fetal status[12].

The co-primary endpoints were time from delivery system administration to vaginal delivery during the first hospitalisation and rate of caesarean delivery[1,12]. Time from delivery system administration to vaginal delivery was significantly shorter for patients who received Mysodelle® versus Propess® (difference between median times: 11.3 hours, see Table 1). The rate of caesarean delivery was not significantly different between treatment arms (see Table 1); non-inferiority of Mysodelle® could not be inferred as the pre-specified confidence interval criteria were not met. Key secondary endpoints also supported the primary outcomes, which are shown in Table 1[1,12].

Table 1. Endpoints from EXPEDITE[1,12]

EXPEDITE	Mysodelle® (n = 678)	Propess® (n = 680)	Treatment difference	p-value
Primary endpoints				
Median time to vaginal delivery, hours (95% CI)*	21.5 (20.0 to 23.4)	32.8 (30.2 to 34.9)	−11.3	< 0.001
Rate of caesarean delivery, % (95% CI)	26.0 (22.7 to 29.4)	27.1 (23.8 to 30.6)	−1.10 (−5.79 to 3.59)	0.65
Key secondary endpoints				
Median time to any delivery (vaginal or caesarean), hours (95% CI)*	18.3 (17.2 to 19.5)	27.3 (26.2 to 28.9)	−9.0	< 0.001
Median time to active labour, hours (95% CI)*†	12.1 (12.0 to 12.9)	18.6 (18.1 to 22.5)	−6.5	< 0.001
Women requiring pre-delivery oxytocin, % (number/n)*	48.1 (324/674)	74.1 (497/671)	−26.0	< 0.001

*women who delivered during the first hospitalisation (14 women who delivered after the first hospitalisation were censored from the time to delivery analyses).
†active labour was defined as progressive cervical dilation to 4 cm with any frequency of contractions or rhythmic, firm, adequate-quality uterine contractions causing progressive cervical change, occurring at a frequency of three or more in ten minutes and lasting ≥ 45 seconds.
CI: confidence interval; n: total number of patients

3.2 Comparative safety

In the EXPEDITE study, adverse events were the reason for caesarean delivery in 97% and 91% of patients receiving caesarean deliveries in the Mysodelle® and Propess® arms, respectively[12]. Adverse events leading to caesarean delivery that occurred in > 1% of patients in either the Mysodelle® or Propess® arms were category II fetal heart rate patterns (9.1% versus 6.2%); uterine tachysystole (≥ 5 contractions in 10 minutes, averaged over three consecutive 10 minute periods) with late decelerations, bradycardia or prolonged decelerations (1.9% versus 0%); arrest of dilation (8.6% versus 12.5%); and descent leading to caesarean delivery (3.5% versus 4.1%)[12].

Overall, there were no significant differences between treatment arms in the proportion of women or neonates who experienced adverse events in the EXPEDITE study[12]. Significantly more women who received Mysodelle® compared to Propess® experienced tachysystole requiring intervention (13.3% versus 4.0%; $p < 0.001$). Other outcomes for which there were significant ($p < 0.05$) differences between the Mysodelle® and Propess® arms were tocolysis use (12.2% versus 4.1%), any tachysystole (adverse event and non-adverse event) (49.1% versus 24.6%) and arrested labour (dilation or descent) (14.2% versus 18.8%)[12]. There were no significant differences between treatment arms in the rate of admission to neonatal intensive care[14]. There were no fetal, maternal or neonatal deaths in the study[12].

3.3 Patient preference survey

The applicant company commissioned an independent online survey to assess women's preference for a shorter induction to delivery duration associated with a higher intensity pain pattern, over a longer induction to delivery duration associated with a lower intensity pain pattern[15]. The survey population consisted of 169 women from the UK, recruited via Facebook advertising, who had given birth by induced labour within the 12-month period prior to completing the survey; of these women, 16.57% were from Wales[15].

Four induction to delivery durations were used (12, 24, 48, or 72 hours) in the survey, with differing associated patterns of pain[15]. Participants were presented with six comparison questions, with all possible combinations of the four scenarios compared against each other. For each question, participants were asked to select their preference from the two labour scenarios presented as graphs, and were then asked to indicate the strength of their preference for their chosen scenario (on a scale of 1–5)[15].

The authors of the survey concluded that women strongly prefer the shorter induction to delivery duration with a higher intensity pain pattern, over a longer induction to delivery duration with a lower intensity pain pattern[15]. This conclusion is statistically valid for the complete sample and also for the Welsh cohort[15].

3.4 AWTTC critique

- Mysodelle® is the first licensed misoprostol preparation for induction of labour in the UK[14]. In practice, short-acting oral misoprostol tablets are sometimes vaginally administered off-label to induce labour. The tablets must be cut or made into suspension to achieve lower doses[14]. Mysodelle® is available for use via health technology appraisal in Scotland for the indication under consideration[16].
- NICE clinical guidelines state that if induction of labour is clinically justified, vaginal prostaglandin E2 as a tablet, gel or controlled-release pessary is usually the preferred method[10]. Whilst the company has only provided comparative evidence versus Propess®, the All Wales Therapeutics and Toxicology Centre (AWTTC)-sought clinical expert opinion indicates that Propess® is likely to be the most relevant comparator.
- In the pivotal study, Mysodelle® significantly reduced the time to vaginal delivery and reduced the need for oxytocin use compared with Propess®[12]. Overall, there were no significant differences in the proportion of patients who experienced adverse events, although there were some differences in individual adverse events experienced by patients receiving the different treatments. The rate of tachysystole with fetal heart rate changes or tachysystole requiring intervention (uterine hyperstimulation) was three times higher with Mysodelle® compared with Propess®[12].
- NICE clinical guidelines state that prostaglandin E2 is the preferred method of induction of labour unless there are specific clinical reasons for not using it (in particular the risk of uterine hyperstimulation)[10]. However, since the original appraisal of Mysodelle® by AWMSG, a NICE surveillance report has been published highlighting new evidence and recommending a partial update of the clinical guidelines; this includes reviewing the recommendations for misoprostol for the induction of labour[10].
- The pivotal study was conducted exclusively in the USA, and therefore patient baseline characteristics and delivery procedure are likely to be different from those in Wales[1]. Furthermore, the study excluded pregnant women aged < 18 years, those whose membranes were ruptured for more than 48 hours before insertion, women with multiple pregnancies, and women with more than three previous vaginal pregnancies after 24 weeks gestation. However, the company highlight that a UK clinical advisory board concluded that overall the results observed with Propess® in the pivotal study were broadly in line with those seen in UK practice[1].
- The reduced time to vaginal delivery associated with use of Mysodelle®, as well as the adverse events arising from either treatment, may impact the women's quality of life. However, the EXPEDITE study did not include any quality of life measurements[12]. Although maternal satisfaction was not captured in EXPEDITE, a new online survey, commissioned by the company, reported that women strongly preferred shorter time in labour with a higher intensity pain pattern, than a longer induction to delivery with a lower intensity pain pattern[15]. Before completing the patient preference survey, women were asked to assume that the outcome of delivering a healthy baby was the same for all scenarios, that the pain

pattern would always be the same for the delivery phase of labour, and that a shorter labour would equate to less time spent in hospital[15]; women did not have to take into account any other factors, including the different safety profiles of the medicines.

- Propess® is licensed for initiation of cervical ripening in women at term (from the 38th week of gestation)[8], whilst Mysodelle® is licensed from the 36th week of gestation and causes cervical ripening and uterine contraction[2]. Mysodelle® is licensed for induction of labour in women with an unfavourable cervix, whilst this restriction does not apply to the Propess® licence[2,8].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The current standard of care in Wales for induction of labour with an unfavourable cervix is Propess®, augmented with oxytocin if required. The original Mysodelle® submission included a CMA, where Mysodelle® and Propess® were considered by the company to be therapeutically equivalent in terms of successful delivery. Following the AWMSG non-recommendation[3], a cost-utility analysis (CUA) using a decision-analytic approach was developed as part of the updated submission[1]. The time horizon is "from hospital admission to discharge". Women enter the model at initiation of therapy with Mysodelle® or Propess®, and proceed to delivery (vaginal or caesarean) during either the first or subsequent hospitalisation. Women exit the model upon successful delivery and resolution of any adverse events[1].

The model adopts an NHS Wales perspective and includes women ≥ 36 weeks gestation, with an unfavourable cervix, in whom induction of labour is clinically indicated[1]. Propess® is licensed for induction of labour from the 38th week of gestation[8]; however, as Mysodelle® is licensed from the 36th week of gestation[2], the economic analysis includes women from the 36th week of gestation[1].

The economic analysis is based on the phase III, randomised, active-controlled EXPEDITE study[1]. This study was conducted in the USA, and there were differences in the distribution of demographic and obstetric characteristics from a Welsh population. However, a UK advisory board commented that the efficacy and safety results obtained in the EXPEDITE study were commensurate with those seen in UK practice for time to delivery, rates of caesarean sections and tachysystole[1].

Welsh treatment patterns are used in the base case analysis, which include time on the antenatal ward, the labour and delivery suite, and the postnatal ward. Treatment patterns in the USA do not include an antenatal ward element, with women being induced in the labour and delivery suite; in comparison, women are induced on the antenatal ward in Wales. The overall duration of hospitalisation is considered to be the same for Wales as the USA, whereby the amount of time to active labour is apportioned to the antenatal ward, as opposed to the labour and delivery suite as in the USA setting. In the EXPEDITE study, mean duration of maternal hospitalisation for women who delivered during the first hospitalisation was [commercial in confidence figures removed] for patients receiving Mysodelle®, and [commercial in confidence figures removed] for those receiving Propess®[17]. The cost of maternal hospitalisation was estimated by calculating a cost per hour using a weighted time spent in each ward or unit. The EXPEDITE study did not differentiate between the mean duration of maternal hospitalisation by vaginal and caesarean delivery; maternal hospitalisation duration is the same regardless of mode of delivery[1].

Other resource-use elements were derived from the EXPEDITE study and include the use of instruments in vaginal deliveries, caesarean delivery, no delivery during first

hospitalisation, use of oxytocin and antibiotics, and neonatal hospitalisation. It is assumed that 5% of women would experience fall out of Propess® and require an additional vaginal insert[18]. No published data were available for the Mysodelle® fall out rate and therefore it was not included. It was assumed that adverse events resulted in caesarean delivery and neonatal adverse events in neonatal admissions; therefore, no additional costs associated with adverse events were included in the analysis.

The unit price used for Mysodelle® was £93, and for Propess® was £33 (Table 6). The unit costs for hospitalisation were taken from a primary research study in a maternity hospital in London[19]; 2008 prices were uplifted to 2015–16 for the analysis[20]. This resulted in a cost per day of £319.65 for an antenatal ward stay, and £1,078.12 for a labour and delivery suite stay. The unit costs included staff salaries, equipment, consumables and capital overheads. The cost of vaginal examinations was included, but additional costs of instrumental delivery or caesarean section were not. The cost of maternal hospitalisation was estimated by calculating a cost per hour weighted by time spent in each ward or unit: £16.56 for Mysodelle® and £16.79 for Propess®.

For women who did not deliver during the first hospitalisation, there was an additional cost of £399.56 for 30 hours on the antenatal ward during the first hospitalisation, on the assumption that the medicine is removed after 24 hours, plus six hours for the use of oxytocin to promote labour.

No utility values were available for women during labour; therefore, it was not possible to quantify the impact of a decreased time in labour on quality of life. A disutility approach was applied, based on caesarean delivery and neonatal intensive care unit admission, for the duration of the hospitalisation using utility values of 0.92 and 0.59 for pain during labour with a vaginal delivery and a caesarean section respectively[21], and 0.7 for a neonatal intensive care unit admission[22].

Sensitivity and scenario analyses test the influence of parameter and structural uncertainty on the robustness of the base case results. These explore the impact of parity status, treatment patterns and costs, as well as the use of two other dinoprostone comparators: Prostin E2® vaginal gel and Prostin E2® vaginal tablets.

4.1.2 Results

The CUA base case results report that Mysodelle® is less costly and is associated with more quality-adjusted life-years (QALYs) than Propess®; thus Mysodelle® dominates Propess® (see Table 2). The cost of maternal hospitalisation accounts for the greatest proportion of costs[1].

Table 2. Results of the base case analysis

	Mysodelle®	Propess®	Difference
Total costs	¶¶	¶¶	¶¶
Total QALYs	¶¶	¶¶	¶¶
ICER (£/QALY gained)	Mysodelle® dominates		

¶¶: commercial in confidence figure removed.
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

The most plausible scenario analyses presented by the company are reported in Table 3. In addition, a one-way sensitivity analysis was conducted to evaluate individual parameter sensitivity using 95% confidence intervals where data permitted, otherwise assigning an arbitrary ± 20% variation[1].

Table 3. Results of scenario analyses[1]

Scenarios	ICER	Plausibility
Scenario 1 Mean hospitalisation duration proportionally adjusted to the Welsh mean length of stay of 3.3 days: ¶¶ for Mysodelle® and ¶¶ with Propess®	Mysodelle® dominates	Mean duration of hospitalisation based on Welsh practice is shorter than that observed in the USA-based EXPEDITE study (¶¶ for Mysodelle® and ¶¶ for Propess® as presented in the base case). This scenario better reflects Welsh treatment practices.
Scenario 2 Prostin E2® gel or tablet as the comparator instead of Propess®	Mysodelle® dominates	It has been assumed that Prostin E2® and Propess® are equally effective. Although Propess® has the largest market share in Wales, Prostin E2® is also used. Assuming 100% Prostin E2® usage does not reflect current practice, and thus does not seem plausible; a scenario with 80% treatment with Propess® and 20% with Prostin E2® gel or tablet would be a more relevant analysis.
Scenario 3 Only statistically significant differences included in the analysis	Mysodelle® is cost saving	Where outcomes are not statistically significantly different in the real world setting, there may be no difference, or the direction of results may change, and so this is useful to support the results.
Scenario 4 Use of NHS reference costs to estimate differences in costs	Mysodelle® dominates	NHS reference costs for induced delivery < 24 hours or > 24 hours are applied. This may be a better reflection of the opportunity costs to the NHS of using Mysodelle®.
AWTTC scenario If unit costs are applied to the antenatal ward, labour and delivery suite, and postnatal ward, and there is no difference in the length of time on the labour and delivery suite, and the postnatal ward for Propess® or Mysodelle®	Mysodelle® cost saving (¶¶)	Unit costs appropriate to each setting are used instead of an average cost based on weighted time on each ward. As the trial was not powered to detect differences in time spent on each ward or unit, this is a useful alternative scenario.
¶¶: commercial in confidence figure removed ICER: incremental cost-effectiveness ratio		

4.1.3 AWTTC critique

The model submitted takes a simplistic, pragmatic approach to economic evaluation. Consequently, the CUA produces crude incremental cost-effectiveness ratio (ICER) estimates. The model inputs for duration of hospitalisation, costs and utility values, which are key model drivers, are associated with limitations and are therefore subject to notable uncertainty. Caution is thus required when interpreting the results of the analyses. These limitations, together with an overview of other key strengths and weaknesses, are explored below:

- The base case CUA seems appropriate given the data available. If women are required to stay in hospital for the duration of induction, then using Mysodelle® appears to be cost saving as the length of labour is shorter with no increase in instrumental deliveries or caesarean sections.
- Estimates of utility gains associated with Mysodelle® are likely underestimated since the lack of available utility values in this patient population means that any quality of life benefits associated with a shorter duration of labour are not captured in the analysis.

- Only utility values relating to mode of delivery and admission to a neonatal unit are considered. Disutility values are applied to the whole hospital stay in the event of a caesarean section or neonatal unit admission. Given that caesarean sections are usually performed due to adverse events relating to the mother or baby, then the disutility applied to the whole hospitalisation is likely to fairly reflect quality of life decrements during that time.
- The use of Mysodelle® led to a higher number of tachysystole events. The model does not capture the effect of this, neither in terms of resource implications due to more intense monitoring nor in terms of the disutility attached to the baby's quality of life. However, this might not be measurable and may be of short duration.
- An average length of stay was applied regardless of mode of delivery; however, it is likely that length of stay is dependent on mode of delivery, with vaginal delivery without instruments requiring a shorter length of stay than caesarean delivery. The EXPEDITE study did not differentiate between the mean duration of maternal hospitalisation by vaginal and caesarean delivery[1]. Rate of caesarean delivery was not statistically significantly different between the two groups (see Table 1).
- The company highlight that the Summary of Product Characteristics for Mysodelle® and Propess® stipulate they should only be used where facilities for continuous fetal and uterine monitoring are available[2,8]. The company submission does not consider the possibility of women being induced as outpatients. However, induction of labour in the outpatient setting is discussed in the NICE guideline[7] and AWTTC-sought clinical expert opinion is that although Mysodelle® is unlikely to be used in this setting, Propess® is currently being used for some outpatient inductions in the UK. Given that the economic argument is based on reducing hospital stay (the time until active labour), if some women are able to return home after a period of monitoring, this would impact on the economic case presented and this scenario could therefore be of relevance.
- A fall out rate of 5% was assumed for Propess® and the associated additional cost was added to the Propess® cost in the base case[1]. In the absence of any published data, the company assumed a 0% fall out rate for the Mysodelle® group[1]. However, the plausibility of this assumption is unclear. When a 5% fall out rate of Mysodelle® is assumed in the base case setting, the total cost for Mysodelle® increases from [commercial in confidence figures removed], and the savings compared to Propess® fall from [commercial in confidence figures removed].

4.2 Review of published evidence on cost-effectiveness

There is a published analysis of a study of resource use of Mysodelle® versus Propess® from a UK healthcare perspective[1,23]. A Markov model was used to estimate clinical outcomes and resource use in a hypothetical cohort of 1,397 pregnant women induced with either Mysodelle® or Propess® at Southmead Hospital, Bristol, UK. Efficacy and safety data were based on the EXPEDITE study. The number of deliveries, proportion of parous to nulliparous women, and hospital management resource use was based on Southmead Hospital clinical data. The analysis indicated that use of Mysodelle® could lead to a 28.9% reduction in the time to vaginal delivery versus use of Propess®. This equated to a 25.2% reduction in the number of midwife shifts and 451 fewer hospital bed days, equating to a potential 27.4% increase in birthing capacity at Southmead hospital. This model-based approach should be interpreted with caution. The authors acknowledge several limitations: the analysis is a theoretical representation of potential clinical practice, medicine costs are not considered, and efficacy data is based on the EXPEDITE study, which was conducted in the USA[23].

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Welsh maternity statistics, there were 33,279 births in Wales in 2015[4]; and 24.9% were induced in 2014–2015[5], resulting in 8,286 induced hospital births in 2015. The company assumes that the number of induced births remains constant over the five years after the introduction of Mysodelle®. Based on sales of Propess®, the company suggests that 70% of induced women receive prostaglandin as their induction agent, equating to 5,801 women being eligible for induction with prostaglandin therapy each year[1]. Company forecasts indicate that Mysodelle® will capture [commercial in confidence figures removed] of the prostaglandin market share in Year 1 and Year 5[1].

The following scenarios were tested:

- 20% variability in market share
- Mysodelle® displacing all products proportionally, rather than only Propess®
- no Propess® fall out
- no adverse event costs (oxytocin and antibiotics)
- 20% variability in secondary care costs.

5.1.2 Results

The estimated net budget impact is presented in Table 4. Taking into account only the net medicines acquisition costs, additional cost burdens of [commercial in confidence figures removed] in Year 1 and Year 5 are anticipated. Whilst medicine acquisition costs lead to an increased budget impact, the base case suggests resource savings ranging from [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 5, attributed to reduced secondary and tertiary care costs and adverse events.

Table 4. Company-reported costs associated with use of Mysodelle® for the induction of labour

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
Number of eligible patients (indication covered in this submission)	5,801	5,801	5,801	5,801	5,801
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Treated patients	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without misoprostol	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market with misoprostol	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figure removed					

In all scenario analyses, the overall net budget impact remained cost saving with Mysodelle® when acquisition costs and resource savings are combined. Resource implications in the budget impact analysis results in cost savings of [commercial in confidence figures removed] from Year 1 to Year 5, of which [commercial in confidence figures removed] were due to reduced adverse events. Cost savings may be realised from net adverse event costs (costs of oxytocin and antibiotics) and secondary or tertiary care costs. Sensitivity analyses were carried out by the applicant company and are reported in Table 5.

Table 5. Company-reported sensitivity analyses of net acquisition and supportive medicine costs with use of Mysodelle® for the induction of labour

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
20% lower market share of new medicine in sub-population	¶¶	¶¶	¶¶	¶¶	¶¶
20% upper market share of new medicine in sub-population	¶¶	¶¶	¶¶	¶¶	¶¶
Mysodelle® displacing all products proportionally, rather than only Propess®	¶¶	¶¶	¶¶	¶¶	¶¶
No Propess® fall-out (one administration only)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of projected births in Wales, rather than remaining constant	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figure removed					

5.1.3 AWTTC critique

- The net financial costs of introducing Mysodelle® in practice may not be equivalent to the opportunity costs calculated for the economic analysis.
- The net secondary and tertiary care savings may not be realised in practice; if so, this would result in a net cost to the NHS following the introduction of Mysodelle® due its higher acquisition cost.
- The costs of secondary care are taken from the cost-utility model and, as such, the limitations of the economic model also apply to the budget impact estimates.

5.2 Comparative unit costs

Acquisition costs for the induction of labour are detailed in Table 6.

Table 6. Examples of acquisition costs of medicines indicated for induction of labour

Regimens	Example doses	Approximate costs per regimen
Mysodelle® 200 microgram vaginal delivery system	One dose over 24 hours	£93
Propess® 10 mg vaginal delivery system	One dose over 24 hours	£33
Prostin E2® 1 mg and 2 mg vaginal gel	One dose (1 mg or 2 mg) followed by a further dose 6 hours later if required	£13 to £27
Prostin E2® 3 mg vaginal tablet	One dose followed by a further dose after 6 hours if required	£13 to £27
Not all regimens may be licensed for use in this patient population. This table does not imply therapeutic equivalence of medicines or doses. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[2,8,24-26]. Costs are based on the Monthly Index of Medical Specialities, and British National Formulary prices as at November 2017[27,28]. Costs of administration and monitoring are not included.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, misoprostol (Mysodelle®) is appropriate for specialist-only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6–12 months[1]:

- An obstetrics clinical group in Scotland is currently working on a publication with data comparing Mysodelle® with Propess® for the induction of labour. It is expected that a submission will be made in the next 6–12 months.
- Obstetric units at King's College, Imperial College, Leeds and Liverpool are auditing the introduction of Mysodelle® into the obstetrics induction of labour service and are expected to start publishing results in the next 6–12 months.
- An Australian study is ongoing: cervical ripening using misoprostol 200 microgram slow-release pessary versus dinoprostone 10 mg slow-release pessary: a randomised, triple-blinded, interventional study comparing safety and efficacy in primiparous women. The estimated completion date is July 2018.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Dates of evidence searches: 23 February 2016, 14 April 2016 and 2 November 2017.
Date range of evidence searches: Date limits were only applied to avoid duplication of previous evidence searches. Evidence was therefore considered for the full date range.

GLOSSARY

Bishop Score

The Bishop score is a group of measurements made by vaginal examination, and is based on the station, dilation, effacement (or length), position and consistency of the cervix[7]. A score of eight or more generally indicates that the cervix is ripe, or favourable; when there is a high chance of spontaneous labour, or response to interventions made to induce labour[7]. In the modified Bishop scoring system, effacement has been replaced by cervical length in centimetres, with reducing length equating to increasing score[29].

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