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Misoprostol (induction of labour) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

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Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BfArM	Federal Institute for Drugs and Medical Devices
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug misoprostol. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 August 2021.

Research question

The aim of this report is to assess the added benefit of misoprostol in comparison with dinoprostone as the appropriate comparator therapy (ACT) for the induction of labour.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of misoprostol

Therapeutic indication	**ACT**[a]
Induction of labour in the presence of an unfavourable cervix[b]	Dinoprostone[c]

a. Presented is the ACT specified by the G-BA.
b. Due to missing clinical data, the SPC recommends its use from the 37th week of pregnancy when the cervix is unfavourable (Bishop score < 7). The G-BA thus assumes that pregnant women who are indicated for induction of labour and have a favourable cervix are not typically eligible for treatment with misoprostol.
c. If mechanical methods for the induction of labour (e.g. balloon catheter) are indicated, they should be allowed in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

Company's approach for deriving added benefit

The check for completeness of the study pool did not reveal any relevant study. The company, in contrast, identified a randomized controlled trial (RCT) by Young et al. 2020 (hereinafter referred to as "Young 2020"). However, this study is unsuitable for assessing the added benefit of misoprostol versus the ACT specified by the G-BA (see Section "Evidence provided by the company" below for more information).

In its dossier, the company explains that misoprostol had originally been approved as an ulcer medication under the trade name Cytotec and was long used off label for inducing labour. According to the company, however, precise dosing of this preparation was impossible, leading

to adverse effects. The preparation was taken off the market as early as in 2006, and the Federal Institute for Drugs and Medical Devices (BfArM) ultimately called for an import stop. The company reports then launching the misoprostol preparation Angusta, whose approval is primarily based on bibliographic sources, particularly a Cochrane review on the use of oral misoprostol for induction of labour.

The company states that, for the present benefit assessment, no RCT conducted by the company is available in this therapeutic indication. The company's information retrieval identified the RCT Young 2020, and the company reports using this study in the 1st step for deriving added benefit. On the basis of the study results, however, the company derived neither greater nor lesser added benefit of misoprostol in comparison with the ACT of dinoprostone. Module 4 A of the company's dossier states that, in a 2nd step, the company discussed and evaluated the added benefit of misoprostol in the context of clinical practice. For deriving added benefit from clinical practice, the company ultimately used selected results from 2 Cochrane reviews on the use of misoprostol for induction of labour. Eventually, the company argues that there is a non-quantifiable added benefit when taking into account long-standing experience regarding the effectiveness of misoprostol for induction of labour and the high, heretofore unmet therapeutic need for an approved, oral misoprostol preparation.

The company's approach is not appropriate. The company concedes that the results from the Cochrane reviews do not meet the requirements for a comparison of oral misoprostol versus the ACT of dinoprostone. The reviews included studies investigating a wide range of pharmaceutical forms, dosages, and dosing regimen for both the employed intervention and the ACT. In addition, a large percentage of the included studies used comparator therapies other than dinoprostone-containing preparations. Young 2020, which the company reportedly used for its benefit assessment, is likewise unsuitable for assessing the added benefit of misoprostol in comparison with the ACT. The reasoning is provided below.

Evidence provided by the company

Design of the Young 2020 study

Young 2020 is an open-label, 3-arm RCT conducted from 1999 to 2000. The study investigated the comparison of oral misoprostol with vaginal misoprostol and with dinoprostone. It included women carrying singleton pregnancies with cephalic presentation (≥ 37 week of pregnancy) and an indication for induction of labour. The pregnant women had to exhibit an unfavourable cervix and no previous uterine surgeries. Treatment with misoprostol or dinoprostone was continued until any of the following events occurred: progression of labour, contraction frequency ≥ 3 in 10 minutes, pathological foetal heart rate, or birth.

Primary outcome of the study was the induction-to-delivery-time interval. Secondary outcomes were morbidity outcomes, health-related quality of life, and adverse events (AEs).

The study arm using vaginal misoprostol is disregarded below since this treatment is not approved in Germany for induction of labour.

Intervention and ACT not implemented in Young 2020

In the study, oral misoprostol was administered at a dose of 50 µg. If necessary, administration was repeated every 4 hours, with the study plan not defining any maximum dose. The study used 100 µg tablets of the Cytotec preparation, split by pharmacy staff. In the comparator arm, dinoprostone vaginal gel was applied intravaginally at a dose of 1 to 2 mg. Where necessary, applications were repeated every 6 hours, again without a maximum dose being defined. The Prostin preparation was used. Neither the intervention used in the study nor the comparator therapy is suitable for answering the research question of the benefit assessment for the following reasons:

- In the Young 2020 intervention arm, the active substance misoprostol was used in the form of split tablets of Cytotec, which the company concedes is not approved in Germany for induction of labour. While the use of an oral dose of 50 µg every 4 hours corresponds to one of the 2 dosing regimens described in the Summary of Product Characteristics (SPC) of the newly approved preparation Angusta (25 µg every 2 hours or 50 µg every 4 hours), there is no proof of bioequivalence of the two misoprostol preparations Cytotec and Angusta. While the company cites a comparative bioequivalence study which, in the company's view, demonstrates comparability of pharmacokinetics and pharmacodynamics of the two preparations (Amini et al. 2020), this conclusion is implausible based on the study-related publication. As Amini et al. conceded, the results of this study did not demonstrate bioequivalence of the two preparations.

  The Young 2020 intervention in the form of the misoprostol preparation Cytotec is therefore unsuitable for adequately representing the intervention relevant for the research question of the present benefit assessment.

- In the Young 2020 comparator arm, the active substance dinoprostone was used in the form of a vaginal gel, the Prostin preparation, which is likewise not approved in Germany for induction of labour.

  The company states that Prostin has been used on the German market in accordance with the SPC of a comparable product. However, as the company concedes in the dossier's Module 3 A, Section 3.1, the comparable preparation to which it refers (Minprostin vaginal gel) is approved on the German market for induction of labour in women with "favourable cervix". According to the company, the preparation therefore does not cover the therapeutic indication relevant for the benefit assessment of misoprostol, i.e. induction of labour in women with unfavourable cervix. All other dinoprostone-containing preparations approved in Germany, some of which being approved even for unfavourable cervix, are available not in the form of a vaginal gel, but in other pharmaceutical forms (Minprostin vaginal tablets; Prepidil [intracervical] gel; Propess vaginal delivery system).

  In addition, the dosing specifications of Prostin and Minprostin differ, particularly with regard to dosing regimen and approved maximum dose. According to the product information, the dinoprostone preparation Prostin used in Young 2020 is dosed higher than Minprostin vaginal gel, which the company describes as comparable. The company

concedes that a BfArM Dear Doctor Letter is available on dinoprostone-containing preparations, which points out stronger warnings regarding the maximum dose and dosing interval of these preparations. For Minprostin, this letter also warns against exceeding the recommended dose or shortening the dosing interval since doing so increases the risk of uterine hyperstimulation, among other things.

All in all, the comparator intervention used in Young 2020 in the form of the dinoprostone preparation Prostin is deemed an inadequate implementation of the ACT.

Summary

In summary, neither the intervention used in the Young 2020 study submitted by the company – split tablets of the misoprostol preparation Cytotec – nor the comparator therapy – the dinoprostone preparation Prostin – adequately reflects the intervention relevant for the present research question and the relevant ACT. Therefore, no suitable data are available for the benefit assessment.

Results

In its dossier, the company does not present any suitable data for assessing the added benefit of misoprostol in comparison with the ACT for induction of labour. Consequently, there is no hint of added benefit of misoprostol comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of misoprostol.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Misoprostol – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Induction of labour in the presence of an unfavourable cervix[b]	Dinoprostone[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Due to missing clinical data, the SPC recommends its use from the 37th week of pregnancy when the cervix is unfavourable (Bishop score < 7). The G-BA thus assumes that pregnant women who are indicated for induction of labour and have a favourable cervix are not typically eligible for treatment with misoprostol.
c. If mechanical methods for the induction of labour (e.g. balloon catheter) are indicated, they should be allowed in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of misoprostol in comparison with dinoprostone as the ACT for the induction of labour.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of misoprostol

Therapeutic indication	**ACT[a]**
Induction of labour in the presence of an unfavourable cervix[b]	Dinoprostone[c]

a. Presented is the ACT specified by the G-BA.
b. Due to missing data, the SPC [3] recommends use from the 37th week of pregnancy when the cervix is unfavourable (Bishop score < 7). The G-BA thus assumes that pregnant women who are indicated for induction of labour and have a favourable cervix are not typically eligible for treatment with misoprostol.
c. If mechanical methods for the induction of labour (e.g. balloon catheter) are indicated, they should be allowed in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The company followed the G-BA's specification of the ACT. In Module 3 A, Section 3.1, of its dossier, the company argues that, in its view, from among the dinoprostone-containing preparations approved in Germany, the drugs Prepidil [4] and Propess [5] are potential comparator therapies because they are approved for induction of labour or cervical ripening in case of an unfavourable cervix. The company's arguments are plausible.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on misoprostol (as of 30 August 2021)
- Bibliographic literature search on misoprostol (most recent search on 21 August 2021)
- Search in trial registries / study results databases on misoprostol (most recent search on 21 August 2021)
- Search on the G-BA website on misoprostol (most recent search on 21 August 2021)

To check the completeness of the study pool:

- Bibliographic literature search on misoprostol (most recent search on 20 September 2021); see Appendix A of the full dossier assessment for search strategies

- Search in trial registries for studies on misoprostol (most recent search on 15 September 2021); see Appendix A of the full dossier assessment for search strategies.
- Viewing of systematic reviews (Cochrane-Reviews [6-8])

No relevant study was identified from the check. The company, in contrast, identified the RCT by Young et al., 2020 [9,10] (hereinafter referred to as Young 2020). However, this study is unsuitable for assessing the added benefit of misoprostol versus the ACT specified by the G-BA (see Section "Evidence provided by the company" below for more information).

Company's approach for deriving added benefit

In its dossier, the company reports that misoprostol had been originally approved as an ulcer medicine under the trade name Cytotec [11], and for a long time, it was used off label for inducing labour. According to the company, however, precise dosing of this preparation was impossible, leading to adverse effects. According to the company, this led to negative reporting and ultimately, in March 2020, to the publication of a Dear Doctor Letter warning against off-label use of the preparation for induction of labour [12]. Eventually, the BfArM called for an import stop for Cytotec in addition to the preparation having been taken off the German market already in 2006. Subsequently, the company launched the misoprostol preparation Angusta [3] on the German market. As described in Module 4 A of the company's dossier, this preparation was approved in Germany in the form of a "full-mixed application" through the mutual recognition procedure, with Denmark as the Reference Member State [13-15]. The approval is based primarily on biographical sources, particularly a Cochrane review on the use of oral misoprostol for induction of labour [6].

The company states that, for the present benefit assessment, no RCT conducted by the company is available in this therapeutic indication. The company's information procurement identified the RCT Young 2020, and the company reports using this study in the 1st step for deriving added benefit. On the basis of the study results, however, the company derived neither greater nor lesser added benefit of misoprostol in comparison with the ACT of dinoprostone. The company reports that for this reason, it did not present a conclusion on the probability of added benefit. Module 4 A of the company's dossier states that in a 2nd step, the company discussed and evaluated the added benefit of misoprostol in the context of clinical practice. The company justifies this approach by the fact that the active substance is established in routine obstetric care and its use has been included in current guidelines [16-18] The company then states that it derived added benefit from clinical practice and, for this purpose, uses selected results from 2 Cochrane reviews on the use of misoprostol for induction of labour from the years 2014 [6] (edited 2018 [7]) and 2021 [8]. Eventually, the company argues that there is a non-quantifiable added benefit when taking into account long-standing experience regarding the effectiveness of misoprostol for induction of labour and the high, heretofore unmet therapeutic need for an approved, oral misoprostol preparation.

The company's approach is not appropriate. The company concedes that the results from the Cochrane reviews do not meet the requirements for a comparison of oral misoprostol versus the ACT of dinoprostone. The reviews included studies investigating a wide range of pharmaceutical forms, dosages, and dosing regimen for both the employed intervention and the ACT. In addition, a large percentage of the included studies used comparator therapies other than dinoprostone-containing preparations. On the basis of the reviews, no studies investigating the comparison of misoprostol with dinoprostone, each in the approved dosing regimen for the investigated pharmaceutical form, were found.

Young 2020, which the company reportedly used in its benefit assessment, is likewise unsuitable for assessing the added benefit of misoprostol in comparison with the ACT. The reasoning is provided below.

Evidence provided by the company

Design of Young 2020

Young 2020 is an open-label, 3-arm RCT conducted from 1999 to 2000. The study investigated the comparison of oral misoprostol with vaginally misoprostol and with dinoprostone. It included women carrying singleton pregnancies with cephalic presentation (≥ 37 week of pregnancy) and an indication for induction of labour. The pregnant women had to exhibit an unfavourable cervix and no previous uterine surgeries.

The Young 2020 study randomized a total of 511 pregnant women, stratified by membrane status (intact/ruptured), to the 3 treatment arms in a 1:1:1 ratio. Treatment with misoprostol or dinoprostone was continued until any of the following events occurred: progression of labour, contraction frequency ≥ 3 in 10 minutes, pathological foetal heart rate, or birth. Further measures taken for induction of labour – such as amniotomy, use of analgesics, or peridural anaesthesia, or the administration of oxytocin – were selected at the discretion of the investigator in charge of the individual pregnant woman following a thorough examination.

Primary outcome of the study was the induction-to-delivery-time interval. Secondary outcomes were morbidity outcomes, health-related quality of life, and AEs.

Detailed information on study design, the employed interventions, and the patient characteristics for the treatment arms on oral misoprostol and dinoprostone of the Young 2020 study are found in Appendix B of the full dossier assessment. The study arm using vaginal misoprostol is disregarded below since this treatment is not approved in Germany for induction of labour.

Intervention and ACT not implemented in Young 2020

In the study, oral misoprostol was administered at a dose of 50 µg. If necessary, administration was repeated every 4 hours, with the study plan not defining any maximum dose. The study used 100 µg tablets of the Cytotec preparation, split by pharmacy staff. In the comparator arm, dinoprostone vaginal gel was applied intravaginally at a dose of 1 to 2 mg. Where necessary,

applications were repeated every 6 hours, again without a maximum dose being defined. The preparation Prostin [19] was used. Neither the intervention used in the study nor the comparator therapy is suitable for answering the research question of the benefit assessment for the following reasons:

- In the Young 2020 intervention arm, the active substance misoprostol was used in the form of split tablets of Cytotec, which the company concedes is not approved in Germany for induction of labour. The use of an oral dose of 50 µg every 4 hours corresponds to 1 of the 2 dosing regimens described in the SPC of the newly approved preparation Angusta (25 µg every 2 hours or 50 µg every 4 hours [3]), but no proof of bioequivalence is available for the 2 misoprostol preparations, Cytotec and Angusta.

  While Module 4 A, Section 4.3.1.1.1 of the company's dossier cites a comparative bioequivalence study in pregnant women with an indication for induction of labour which, in the company's view, demonstrates the comparability of the 2 drugs' pharmacokinetics and pharmacodynamics (Amini et al. 2020 [20]), this conclusion is implausible based on the study-related publication. The study compared the oral application of the two preparations at 2 different doses (25 µg and 50 µg) as well as the sublingual application of 1 dose (50 µg). According to the study plan, bioequivalence was assumed to exist if the 90% confidence intervals of effect estimators for the examined pharmacokinetics parameters were within a range of 80% to 125%. Regardless of dosage and pharmaceutical form, none of the comparisons of the preparations were within these limits. As conceded by Amini et al., therefore, the results of this study did not demonstrate bioequivalence of the two preparations.

  The Young 2020 intervention in the form of the misoprostol preparation Cytotec is therefore unsuitable for adequately representing the intervention relevant for the research question of the present benefit assessment.

- In the Young 2020 comparator arm, the active substance dinoprostone was used in the form of a vaginal gel, the Prostin preparation, which is likewise not approved in Germany for induction of labour.

  Module 4 A, Section 4.3.1.2.1.1 of the company's dossier states that the Young 2020 study used Prostin in accordance with the associated product information [19] and in compliance with the recommendations of the S2k guideline (induction of labour) relevant for the German healthcare context [16] as well as the SPC of a comparable product on the German market [21].

  The company's arguments are not plausible. The S2k guideline for induction of labour does not include any dosing recommendations for dinoprostone-containing preparations. As the company concedes in the dossier's Module 3 A, Section 3.1, the comparable product which it cites (Minprostin vaginal gel [21]) is approved on the German market for induction of labour in "favourable cervix". According to the company, the preparation therefore does not cover the therapeutic indication relevant for the benefit assessment of

misoprostol, i.e. induction of labour in women with unfavourable cervix. All other dinoprostone-containing preparations approved in Germany, some of which being approved even for women with unfavourable cervix, are available in pharmaceutical forms other than a vaginal gel (Minprostin vaginal tablets [22]; Prepidil [intracervical] gel; Propess vaginal release system [5]).

In addition, the dosing specifications for Prostin and Minprostin differ, particularly with regard to dosing regimen and approved maximum dose, as demonstrated by a comparison of the respective product information, including SPC:

- Prostin [19]
  - Starting dose of 2 mg in primiparae with Bishop score ≤ 4; 1 mg for all other women giving birth
  - Depending on progress of induction, after 6 hours, a subsequent dose of 2 mg or 1 mg, respectively
  - Maximum dose of 4 mg for primiparae with unfavourable cervix or 3 mg for other patients
- Minprostin vaginal gel [21]
  - Starting dose of 1 mg
  - Depending on progress of birth, a subsequent dose of 2 mg or 1 mg, respectively
  - Maximum dose of 3 mg in 24 hours

As per product information, the dinoprostone preparation Prostin is hence dosed higher in primiparae than Minprostin vaginal gel, which the company describes as comparable. Consequently, the primiparae included in Young 2020, which make up more than 60% of the study population (see Table 12 in Appendix B of the full dossier assessment), might potentially have received too high a dose. There is a paucity of information on the actual dosages administered in the study. The study publication states that the pregnant women received 1 to 2 mg per dose. The median number of Prostin doses received was 2 doses, and the maximum 6 doses. This departs from the Minprostin dosing specifications. As described above, the SPC specifies only a starting dose of 1 mg and a maximum dose of 3 mg in 24 hours. In Module 4 A, Section 4.3.1.2.1.1 of the dossier per se, the company concedes that the available information does not permit an assessment of doses taken in excess of the maximum daily dose during the interventions used in Young 2020.

In Module 3 A, Section 3.2.2, the company also points out that a Dear Doctor Letter by BfArM is available on dinoprostone-containing preparations [23], pointing out warnings regarding the maximum dose and dosing interval of these preparations. For Minprostin, this letter also warns against exceeding the recommended dose or shortening the dosing interval since doing so increases the risk of uterine hyperstimulation, among other things.

All in all, the comparator intervention used in Young 2020 in the form of the dinoprostone preparation Prostin is deemed an inadequate implementation of the ACT.

Irrespective of the fact that the intervention and comparator therapies used in Young 2020 are unsuitable for answering the research question of the benefit assessment, the following additional uncertainties exist:

- Young 2020 likewise did not define a maximum dose for the use of the misoprostol preparation Cytotec. For the newly approved preparation Angusta, however, the maximum dose is 200 µg within 24 hours as per SPC. Like for the employed comparator therapy, the study provides little information on the Cytotec dosage used. The study publication states that a median of two 50 µg doses and a maximum of 11 doses were administered. On the basis of the available information, it therefore remains unclear whether the Cytotec maximum dose of 200 µg within 24 hours was exceeded in a relevant percentage of pregnant women.
- In Young 2020, Cytotec was administered in the form of split tablets. As the company concedes in the dossier's Module 4 A, Section 4.3.1.1.2, splitting can lead to imprecise drug concentrations and thereby jeopardize correct dosing of the active substance misoprostol. Similarly, in a Dear Doctor Letter on risks of the off-label use of Cytotec for induction of labour [12], the BfArM points out that Cytotec tablets are not designed to be split, and that correct dosing thus cannot be ensured with split tablets. Referencing a pertinent investigation by Berard et al., 2014 [24], the company adds that, due to the moisture sensitivity of misoprostol, cutting Cytotec tablets is associated with the risk of the misoprostol concentration decreasing in the parts of the tablet exposed to air. The use of split Cytotec tablets in the Young 2020 intervention arm therefore risks a mismatch between the dosing of misoprostol and the approved Angusta dosing.
- As described above, according to its SPC [21], the dinoprostone preparation Minprostin vaginal gel is approved for pregnant women with favourable cervix. Sufficient favourability is defined as a Bishop score ≥ 4. Hence, the cutoff for a sufficiently favourable cervix is slightly lower for Minprostin vaginal gel than defined in therapeutic indication of misoprostol. As per the SPC of the misoprostol preparation Angusta, insufficiently favourable cervix is defined as a Bishop score < 7, and conversely, a favourable cervix would be at a Bishop score ≥ 7.

  Most of the pregnant women included in Young 2020 had an unfavourable cervix (average Bishop score of about 4). However, using the Bishop score as the sole criterion, the use of Minprostin vaginal gel for induction of labour as per the SPC would be an option only for pregnant women with a Bishop score of 4 or higher. Consequently, only part of the study population would be covered by the therapeutic indication of Minprostin vaginal gel. Against this background, the company's approach of comparing the Prostin preparation used in the study with Minprostin vaginal gel is inappropriate.

Summary

In summary, neither the intervention used in the Young 2020 study submitted by the company – split tablets of the misoprostol preparation Cytotec – nor the comparator therapy – the dinoprostone preparation Prostin – adequately reflects the intervention relevant for the present research question and the relevant ACT. Therefore, no suitable data are available for the benefit assessment.

2.4 Results on added benefit

In its dossier, the company does not present any suitable data for assessing the added benefit of misoprostol in comparison with the ACT for induction of labour. Consequently, there is no hint of added benefit of misoprostol comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the results of the benefit assessment of misoprostol in comparison with the ACT.

Table 5: Misoprostol – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Induction of labour in the presence of an unfavourable cervix[b]	Dinoprostone[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Due to missing data, the SPC [3] recommends use from the 37th week of pregnancy when the cervix is unfavourable (Bishop score < 7). The G-BA thus assumes that pregnant women who are indicated for induction of labour and have a favourable cervix are not typically eligible for treatment with misoprostol.
c. If mechanical methods for the induction of labour (e.g. balloon catheter) are indicated, they should be allowed in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The above assessment deviates from that by the company, which derived a non-quantifiable added benefit of misoprostol in comparison with the ACT.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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