Gemeinsamer Bundesausschuss

Justification

of the Draft Resolution of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Misoprostol (labour induction)

of 17 February 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The medicinal product Angusta, containing the active ingredient misoprostol, was first placed on the market on 1 September 2021. Relevant date according to Chapter 5, Section 8, paragraph 1, number 7 of the Rules of Procedure of the G-BA (VerfO) for the start of the evaluation procedure for the active ingredient misoprostol is within three months of the request by the G-BA. If the medicinal product has not yet been placed on the market at that time, the procedure shall start on the date on which it is first placed on the market.

According to Section 35a paragraph 6 SGB V, the G-BA can also initiate a benefit assessment according to Section 35a paragraph 1 SGB V for reimbursable medicinal products with an active ingredient that is not a new active ingredient according to Section 35a paragraph 1 SGB V, if a new marketing authorisation with new dossier protection is granted for the medicinal product. The therapeutic indication of the medicinal product Angusta with the active ingredient misoprostol "for induction of labour" differs from the therapeutic indications of the

already approved proprietary medicinal products with the active ingredient misoprostol with regard to the patient population and thus, refers to a different patient population. A new dossier protection was granted for the medicinal product Angusta with the active ingredient misoprostol.

Therefore, at its session on 3 September 2020, the Federal Joint Committee (G-BA) decided to initiate a benefit assessment according to Section 35a, paragraph 1 SGB V for the active ingredient misoprostol in the therapeutic indication of induction of labour according to Section 35a, paragraph 6 SGB V in conjunction with Chapter 5, Section 16, paragraph 1 VerfO.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 August 2021. On 1 September 2021, the assessment procedure started.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 December 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of misoprostol compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of misoprostol.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Misoprostol (Angusta) according to product information

Angusta is used to induce labour.

Therapeutic indication of the resolution (resolution of 17.02.2022):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Pregnant women with indication for induction of labour in case of unfavourable cervix (Bishop score < 7)

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy:

- Dinoprostone

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In the therapeutic indication, the following approved medicinal products are suitable for the induction of labour: dinosprostone (prostaglandin E2), oxytocin.

on 2. For the induction of labour, the following non-medicinal procedures are generally considered: membrane sweeping, amniotomy, balloon catheter, hygroscopic dilators

on 3. In the mentioned therapeutic indication, there are no resolutions approved by the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V or non-medicinal treatments.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

The evidence available in the therapeutic indication is limited and relates to both mechanical interventions and pharmacological options for induction of labour.

An analysis of the available evidence identified a Cochrane review of the safety and efficacy of membrane sweeping, a non-medicinal method of induction of labour. The studies compared vaginal and intracervical prostaglandin administration (4 studies),

intravenous oxytocin with and without amniotomy (1 study), and vaginal and oral misoprostol[2] (2 studies).

A Cochrane review was also included on the efficacy and safety of mechanical methods of induction of labour compared with dinoprostone (prostaglandin E2, vaginal and intracervical), low-dose misoprostol (oral and vaginal), amniotomy or oxytocin. A Cochrane review assessing the benefits and harms of different methods of induction of labour in women who have previously had a caesarean section was also included.

Also included was a systematic review assessing the efficacy of oral misoprostol for induction of labour versus prostaglandin E2 vaginal gel, versus oxytocin infusion, and versus balloon catheters. Another included systematic review compares the safety and efficacy profile of the balloon catheter for cervical ripening to different dosage and administration regimens of misoprostol.

In addition to a New Zealand guideline, the German S2k guideline on induction of labour was also included. Although this guideline does not sufficiently fulfil the methodological requirements, it was presented additionally due to its relevance for the German health care context.

For pregnant women with an indication for induction of labour with an unfavourable cervix, the only approved medicinal option is dinoprostone (prostaglandin E2). Oxytocin is contraindicated for this patient population with unfavourable cervix.

In the overall analysis of the available evidence, the G-BA considers the approved medicinal option dinoprostone to be an appropriate comparator therapy for the comparison with misoprostol.

Based on the available evidence on the efficacy of mechanical methods for induction of labour, it should be noted that any mechanical therapy options (e.g., balloon catheters) indicated should be made available to women. In clinical practice, any mechanical methods indicated are used simultaneously as well as sequentially. As part of a study, it must be documented which additional measures for induction of labour (simultaneous and sequential) are used.

Taking into account the information in the product information in section 4.2 "Due to lack of clinical data, the use of Angusta is recommended from the 37th week of pregnancy if the cervix is inadequately favourable (Bishop score < 7)", the G-BA concludes that pregnant women with an indication for induction of labour with a favourable cervix are not usually eligible for a treatment with misoprostol. Accordingly, an appropriate comparator therapy is not separately determined.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of misoprostol is assessed as follows:

[2] A medicinal product and dosing scheme not approved for the therapeutic indication in Germany were administered.

Pregnant women with indication for induction of labour in case of unfavourable cervix (Bishop score < 7)

An additional benefit is not proven.

Justification:

In order to derive the additional benefit, the pharmaceutical company uses selected results from two Cochrane reviews on the use of misoprostol in the induction of labour. The reviews included studies that examined a wide variety of dosage forms, dosages and dosing schemes for both the intervention and the comparator therapy used. Moreover, in addition to dinoprostone-containing preparations, other comparator therapies were also used in a large percentage of the included studies. Thus, the results from the Cochrane reviews do not meet the requirements for a comparison of oral misoprostol versus the appropriate comparator therapy dinoprostone.

Furthermore, the pharmaceutical company does not submit any randomised controlled trial (RCT) conducted by it in the therapeutic indication as part of the benefit assessment. Instead, it identifies the study by Young et al. 2020 (hereafter Young 2020) to derive the additional benefit.

The Young 2020 study was an open-label, 3-arm RCT conducted from 1999 to 2000. The study investigates the comparison of oral misoprostol with vaginal misoprostol or with dinoprostone. The study arm on the vaginal use of misoprostol is not considered further in the following, as it is not approved for induction of labour in Germany.

The study enrolled pregnant patients with a singleton in the cranial position (≥ 37th week of pregnancy) who had an indication for induction of labour. Pregnant women should have an unfavourable cervix and no previous uterine surgery.

The primary endpoint of the study was the induction-to-delivery interval. Secondary endpoints were the endpoints of morbidity, health-related quality of life and adverse events (AEs).

In the intervention arm of the Young 2020 study, the active ingredient misoprostol was used in the form of split tablets of the Cytotec preparation, which is not approved in Germany for use in induction of labour. The use of an oral dose of 50 µg every four hours corresponds to one of the two dosing schemes described in the product information of the newly approved preparation Angusta (25 µg every two hours or 50 µg every four hours), but there is no evidence of bioequivalence between the two misoprostol preparations Cytotec and Angusta.

The intervention used in the Young 2020 study in the form of the misoprostol Cytotec preparation is therefore not suitable to adequately represent the intervention relevant to the research question of the present benefit assessment.

In the comparator arm of the Young 2020 study, the active ingredient dinoprostone was used in the form of a vaginal gel of the Prostin preparation, which is also not approved in Germany for use in induction of labour. However, the comparable product on the German market, Minprostin Vaginal Gel, for induction of labour in the case of "sufficient favourability of the uterine cervix" does not cover the indication of induction of labour in unfavourable cervix

(Bishop score < 7) that is relevant for the benefit assessment of misoprostol. In addition, the dosage specifications of the Prostin and Minprostin preparations differ in particular with regard to the dosing scheme and the permitted maximum dose.

The comparator intervention used in the Young 2020 study in the form of the dinoprostone Prostin preparation is therefore not considered to be an adequate implementation of the appropriate comparator therapy overall.

In summary, it can be stated that neither the intervention nor the comparator therapy used in the Young 2020 study is suitable to adequately represent the intervention and appropriate comparator therapy relevant for the present benefit assessment.

There are no suitable data available for the benefit assessment.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Angusta with the active ingredient misoprostol. Angusta is used to induce labour.

The Federal Joint Committee determined dinoprostone as the appropriate comparator therapy.

To derive the additional benefit, the pharmaceutical company uses select results from two Cochrane reviews on the use of misoprostol in the induction of labour, which, however, are not suitable for the benefit assessment due to different dosage forms, dosages and dosing schemes for both the intervention and the comparator therapy used. Moreover, in addition to dinoprostone-containing preparations, other comparator therapies were also used in a large percentage of the included studies.

Furthermore, the pharmaceutical company submits the open-label, 3-arm, randomised controlled trial (RCT) by Young et al. 2020 (hereinafter Young 2020), which compares orally taken misoprostol with vaginally applied misoprostol or with dinoprostone.

In the intervention arm of the Young 2020 study, the active ingredient misoprostol was used in the form of split tablets of the Cytotec preparation, which is not approved in Germany for use in induction of labour. There is no evidence of bioequivalence between the two misoprostol Cytotec and Angusta preparations.

In the comparator arm of the Young 2020 study, the active ingredient dinoprostone was used in the form of a vaginal gel, the Prostin preparation, which is also not approved in Germany for use in induction of labour. However, the comparable product on the German market, Minprostin Vaginal Gel, for induction of labour in the case of "sufficient favourability of the uterine cervix" does not cover the indication of induction of labour in unfavourable cervix (Bishop score < 7) that is relevant for the benefit assessment of misoprostol.

In summary, it can be stated that neither the intervention nor the comparator therapy used in the Young 2020 study is suitable to adequately represent the intervention and appropriate comparator therapy relevant for the present benefit assessment.

In the overall assessment, it is found that an additional benefit is not proven for misoprostol in pregnant women with an indication for induction of labour with an unfavourable cervix (Bishop score < 7).

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The pharmaceutical company relates the percentage of patients in the SHI target population, obtained from the federal evaluation of quality indicators and key figures for obstetrics by the Institute for Quality Assurance and Transparency in Health Care (IQTIG) from the assessment year 2019, to the data on the width of the cervix at the time of inpatient admission for all pregnant women with late vaginal delivery and not exclusively to women in whom the birth was induced. It can be assumed that not all of these women fulfilled the indications for induction of labour. Therefore, the transferability of this percentage is subject to uncertainty. On the other hand, it should be noted that the pharmaceutical company also includes women in the population, for whom no information on the width of the cervix is available, for the calculation of the percentage of patients in the SHI target population. This tends to lead to an underestimation of the proportion value, since the women with missing information on the width of the cervix are thus completely assigned to the group with a cervical width > 5 cm. Furthermore, the derivation does not take into account the restriction to pregnant women from the 37th week of pregnancy.

An additional determination of the proportion values of patients with the relevant contraindication "caesarean section in a previous birth" in the SHI target population results in a proportion of 15% of multiparous women with a caesarean section in a previous birth from a population of primiparous and multiparous women. This reduces the number of calculated patients in the SHI target population by 15%.

Against the background of the available data, the upper and lower limits of the number of patients in the SHI target population are subject to uncertainties.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account.

Treatment with misoprostol should only be initiated and monitored by specialists experienced in the treatment of pregnant women with an indication for induction of labour in the case of unfavourable cervix (Bishop score < 7). It should only be administered by trained medical professionals in a hospital where there are facilities for continuous monitoring of the foetus and uterus

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2022).

For the cost calculation, a maximum treatment duration of 24 hours is assumed.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Misoprostol - tablets	25 µg orally every 2 hours or 50 µg orally every 4 hours	1	1	1
Appropriate comparator therapy				
Pregnant women with indication for induction of labour with unfavourable cervix (Bishop score < 7)				
Dinoprostone - vaginal gel	0.5 mg (initial) or 0.5 mg (initial) and 0.5 mg (after 8 - 12 hours) or 0.5 mg (initial) and 0.5 mg (after 8 - 12 hours) and 0.5 mg (after 8 - 12 hours)	1	1	1

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Misoprostol	25 – 50 µg	25 – 200 µg	1 – 8x25 µg or 1 – 4x50 µg	1	1-8 x 25 µg
Appropriate comparator therapy					
Pregnant women with indication for induction of labour in case of unfavourable cervix (Bishop score < 7)					
Dinoprostone - vaginal gel	0.5 mg	0.5 mg - 1.5 mg	0.5 mg – 1.5 mg	1	0.5 mg – 1.5 mg (1-3 gels)

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
			(1-3 gels)		

Costs:

Costs of the medicinal products:

Misoprostol and dinoprostone are listed in the LAUER-TAXE®, but are only dispensed as clinic packs. Accordingly, the active ingredients are not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply.

The calculation is based on the purchase price of the clinic pack plus 19% value added tax, in deviation from the LAUER-TAXE® data usually taken into account.

Designation of the therapy	Packaging size	Costs (Taxe® clinic purchase)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Misoprostol - tablets	8 TAB	€ 98.30	€ 18.68	€ 116.98
Appropriate comparator therapy				
Dinoprostone - vaginal gel	1 x 2.5 ml GEL	€ 34.51	€ 6.56	€ 41.07
Abbreviations: TAB = tablets; VRS = vaginal release system				

LAUER-TAXE® last revised: 1 February 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 23 March 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 August 2021, the pharmaceutical company submitted a dossier for the benefit assessment of misoprostol to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 7 VerfO.

By letter dated 31 August 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient misoprostol.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2021. The deadline for submitting written statements was 22 December 2021.

The oral hearing was held on 10 January 2022.

By letter dated 12 January 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 28 January 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 February 2022, and the proposed resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	23 March 2021	Determination of the appropriate comparator therapy
Working group Section 35a	4 January 2022	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal product	10 January 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 January 2022 1 February 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	8 February 2022	Concluding discussion of the draft resolution
Plenum	17 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 February 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken