Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Isoflurane (sedation of mechanically ventilated patients during intensive care)

of 21 July 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 Sedaconda, containing the active ingredient isoflurane, was first placed on the market on 1 February 2022. 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 isoflurane 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 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 Sedaconda with the active ingredient isoflurane "for sedation of mechanically ventilated patients during intensive care" differs from the therapeutic indications of the already approved proprietary medicinal products with the active ingredient isoflurane with regard to the patient population and thus, refers to a different patient population. A new dossier protection was granted for the medicinal product Sedaconda with the active ingredient isoflurane.

Therefore, at its session on 17 September 2020, the Federal Joint Committee (G-BA) decided to initiate a benefit assessment for the active ingredient isoflurane in the indication sedation of mechanically ventilated adult patients during intensive care according to Section 35a, paragraph 6 SGB V in conjunction with Chapter 5, Section 16, paragraph 1 VerO.

The final dossier was submitted to the G-BA in due time on 31 January 2022. On 1 February 2022, 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 2 May 2022, 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 isoflurane compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

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 isoflurane.

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 isoflurane (Sedaconda) in accordance with the product information

Sedaconda is used for sedation of mechanically ventilated adult patients during intensive care.

Therapeutic indication of the resolution (resolution of 21.07.2022):

see the approved therapeutic indication

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Mechanically ventilated adult patients for whom sedation is indicated

Appropriate comparator therapy for isoflurane:

A therapy according to doctor's instructions under consideration of propofol, midazolam and dexmedetomidine

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 patient-relevant benefit has already been determined by the G-BA 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 present therapeutic indication, the active ingredients dexmedetomidine, midazolam and propofol are generally approved for the sedation of patients undergoing intensive medical treatment.

on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy for the indication to be assessed.

on 3. In the therapeutic indication under consideration here, no resolutions of the G-BA are available.

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.

According to the current guideline "Analgesia, Sedation and Delirium Management in the Intensive Care Unit" (DAS guideline 2015), the use of propofol should be considered for sedation in invasively ventilated patients. In addition, according to the guideline, inhaled sedatives and the benzodiazepine midazolam can be used. However, apart from the active ingredient isoflurane to be assessed, no other inhaled sedatives are approved in the present indication. Results of systematic reviews indicate that in the present indication the use of the active ingredient dexmedetomidine is associated with a lower risk of delirium compared with the active ingredients propofol and midazolam.

Thus, it cannot be deduced from the current evidence that the active ingredients approved and recommended in the indication are to be regarded as equally appropriate treatment options. Rather, the treatment decision is made according to the treating physician. The active ingredients propofol, midazolam and dexmedetomidine should therefore be available as part of a study. Accordingly, the G-BA has determined a therapy according to doctor's instructions under consideration of propofol, midazolam and dexmedetomidine.

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 isoflurane is assessed as follows:

For mechanically ventilated adult patients for whom sedation is indicated, an additional benefit of isoflurane compared to the appropriate comparator therapy is not proven.

Justification:

For the assessment of the additional benefit of isoflurane, the pharmaceutical company presents the randomised, open-label SED001 study, in which isoflurane was compared to propofol. 301 mechanically ventilated adult patients who had received propofol for sedation for up to 48 hours prior to randomisation and who continued to have a clinically probable indication for sedation for at least 24 hours at the time of randomisation, as well as a target sedation depth according to the Richmond Agitation Sedation Score (RASS) in a range from -1 (light sedation) to -4 (deep sedation) were enrolled in the study.

Treatment with the study medication was limited to 48 hours (± 6 hours). After 24 hours and after 48 hours, a wake-up test was carried out in each case, with the possibility of extubation, depending on the condition of the patients. After the end of the study treatment, patients with a need for further sedation received standard local treatment. The duration of observation was up to 30 days, depending on the endpoint. The primary endpoint of the study was the time interval over which the prescribed sedation level was maintained. The study was conducted in Germany and Slovenia between July 2017 and February 2020.

The patients in the SED001 study were treated with the study medication for a maximum of 48 ± 6 hours. According to the pharmaceutical company, the patients received sedation

according to the local standard if sedation was indicated again after the end of treatment with the study medication or after a break. This procedure resulted in a change of sedative for some of the study participants.

The information provided by the pharmaceutical company does not show how many patients were sedated beyond the treatment duration with the study medication and over what period of time these patients were continuously sedated. However, based on the evaluations of the endpoint duration of ventilation, for example, which included 117 and 123 patients in the isoflurane and propofol arms, respectively, it can be deduced that a relevant percentage of patients were ventilated with the study medication beyond the treatment duration. For example, 20% of patients had a maximum of 2 ventilator-free days during the entire 30-day study period. Similarly, only 55 and 63 of the patients in the isoflurane and propofol arms, respectively, were extubated by the end of treatment with the study medication. It can therefore be assumed that for a relevant percentage of the patients enrolled in the study, an indication for ventilation and thus, also for sedation existed even after the treatment duration with the study medication.

The predefined treatment duration of 48 ± 6 hours with the study medication consequently covers only a part of the actual sedation period for a relevant percentage of the patients enrolled in the study. Furthermore, the switch to the local standard therapy following the study medication must be viewed critically, especially in the isoflurane arm, as sedation with isoflurane is not limited to a certain period of time according to the product information. In addition, it cannot be assumed that a change of sedative without an identifiable reason is in line with the healthcare context.

For the above reasons, the SED001 study is not suitable for the present benefit assessment. The benefit assessment would require data covering the use of the study medication over the entire sedation period until extubation, including sufficiently long follow-up of patient-relevant endpoints.

In its written statement, the pharmaceutical company did not submit any study data that could be used for the benefit assessment.

In the overall assessment, the study cannot be used for the benefit assessment for the reasons mentioned and no suitable data are available to assess the additional benefit of isoflurane compared to the appropriate comparator therapy. An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the known active ingredient isoflurane. Isoflurane is approved for sedation of mechanically ventilated adult patients during intensive care. The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions under consideration of propofol, midazolam and dexmedetomidine.

To derive the additional benefit, the pharmaceutical company uses the randomised, open-label SED001 study, in which isoflurane was compared to propofol.

The SED001 study is not suitable for the benefit assessment due to the limitation of the treatment duration with the study medication to 48 ± 6 hours and the subsequent switch to a standard local treatment in patients with a need for further sedation. The predefined treatment duration with the study medication of 48 ± 6 hours covers only a part of the actual sedation period for a relevant percentage of the patients enrolled in the study. Furthermore, the switch to the local standard therapy following the study medication must be viewed critically, especially in the isoflurane arm, as sedation with isoflurane is not limited to a certain period of time according to the product information. In addition, it cannot be assumed that a change of sedative without an identifiable reason is in line with the healthcare context.

In the overall assessment, there are no suitable data for the assessment of the additional benefit of isoflurane compared with the appropriate comparator therapy. An additional benefit is not proven.

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 G-BA bases its resolution on the estimate of patient numbers derived by the pharmaceutical company in the dossier. Overall, the derivation of patient numbers is comprehensible, but subject to uncertainty.

When calculating the number of coded OPS (operation and procedure) codes for mechanical/ invasive ventilation per year as a mean value in the period from 2010 to 2020, the selected coded OPS codes may lead to multiple counts and, where applicable, counts that were not coded for the purpose of mechanical ventilation. In addition, there are uncertainties in calculating the percentage of mechanically/ invasively ventilated patients who also receive sedation. Overall, the calculated lower limit is uncertain and the upper limit tends to be overestimated.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account.
Treatment with Sedaconda should only be initiated and monitored by medical specialists experienced in the treatment of mechanically ventilated patients, the Sedaconda Anaesthetic Conserving Device (ACD) delivery system, and the pharmacodynamic properties of isoflurane.

Sedaconda must only be delivered via Sedaconda ACD, as the efficacy and safety of inhaled isoflurane sedation have only been established with Sedaconda ACD. Sedaconda must only be used in intubated or tracheotomised patients with a secure airway.

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 July 2022).

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Treatment period:

The treatment period for sedation of mechanically ventilated patients during intensive care is different from patient to patient and depends on the underlying disease and the recovery process. An average length of stay of 3.8 days[2] in the intensive care unit in Germany is used as an approximation of the average sedation duration. However, the average sedation duration may differ from the average length of stay in the intensive care unit used as a basis. The G-BA also assumes on the basis of the data from the SED001 study that a longer treatment duration may be indicated for a relevant percentage of patients in the therapeutic indication.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Isoflurane	1 x daily, on 3.8 days[2]	1	3.8	3.8
Appropriate comparator therapy				
Propofol	1 x daily, on 3.8 days[2]	1	3.8	3.8
Dexmedetomidine	1 x daily, on 3.8 days[2]	1	3.8	3.8
Midazolam	1 x daily, on 3.8 days[2]	1	3.8	3.8

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).

The dosage of isoflurane depends on the patient's respiratory minute volume. For the presentation of the therapy modes, the average maintenance dose in the product information is used as a basis. The presentation of the dose titration is omitted as this is different from patient to patient.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption/ treatment day[3]	Treatment days/ patient/ year	Average annual consumption
Medicinal product to be assessed					
Isoflurane	3 ml/h - 14 ml/h over 24 h	72 ml - 336 ml	72 ml – 336 ml	3.8	273.6 ml - 1,276.8 ml (3 - 13 x 100 ml)

[2] DESTATIS. Health. Basic hospital data 2017 (2018); https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Krankenhaeuser/Publikationen/Downloads-Krankenhaeuser/grunddaten-krankenhaeuser-2120611177004.pdf?__blob=publicationFile

[3] As this is a continuous sedation, the consumption per treatment day (24 hours each) is calculated on a pro-rata basis and not in whole units.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption/ treatment day[3]	Treatment days/ patient/ year	Average annual consumption
Appropriate comparator therapy					
Propofol	0.3 mg/kg bw/h = 23.1 mg/h - 4 mg/kg BW/h = 308 mg/h	554.4 mg - 7,392 mg	554.4 mg - 7,392 mg	3.8	2,106.7 mg (1 x 200 mg + 4 x 500 mg) - 28,089.6 mg (28 x 1,000 mg + 1 x 200 mg)
Dexmedetomidine	0.2 µg/kg BW/h = 15.4 µg/h - 1.4 µg/kg BW/h = 107.8 µg/h	369.6 µg - 2,587.2 µg	369.6 µg - 2,587.2 µg	3.8	1,404.5 µg (4 x 400 µg) - 9,831.4 µg (10 x 1,000 µg)
Midazolam	0.03 mg/kg BW/h = 2.31 mg/h - 0.2 mg/kg BW/h = 15.4 mg/h	55.44 mg - 369.6 mg	55.44 mg - 369.6 mg	3.8	210.7 mg (4 x 50 mg + 1 x 15 mg) - 1,404.5 mg (1 x 5 mg + 28 x 50 mg)

Costs:

Costs of the medicinal products:

The therapeutic indication of isoflurane restricts the use of the medicinal product, as well as the use of the active ingredients of the appropriate comparator therapy, to the inpatient setting. This is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. In addition, no additional charges are incurred for isoflurane and for the active ingredients of the appropriate comparator therapy.

Since the costs of medicinal products are currently reimbursed within the framework of the flat-rate inpatient reimbursement system (Diagnosis Related Groups, DRG) in the SHI system, the calculation is based approximately on the SPC (sales price of the pharmaceutical company) plus a VAT rate of 19%. The actual costs incurred by the hospital may vary from hospital to hospital.

Designation of the therapy	Packaging size	Cost (manufacturer's sales price)	Value added tax (19%)	Costs of the medicinal product[4]
Medicinal product to be assessed				
Isoflurane 1 ml	600 INH	€ 489.36	€ 92.98	€ 582.34
Appropriate comparator therapy				
Propofol 200 mg	SIJ	€ 14.27	€ 2.71	€ 16.98
Propofol 500 mg	SIJ	€ 75.95	€ 14.43	€ 90.38
Propofol 1000 mg	SIJ	€ 150.31	€ 28.56	€ 178.87
Dexmedetomidine hydrochloride 0.473 mg	1600 CIS	€ 100.00	€ 19.00	€ 119.00
Dexmedetomidine hydrochloride 1.182 mg	4000 CIS	€ 260.00	€ 49.40	€ 309.40
Midazolam 50 mg	500 IIS	€ 36.90	€ 7.01	€ 43.91
Midazolam 15 mg	150 IIS	€ 12.60	€ 2.39	€ 14.99
Midazolam 5 mg	50 IIS	€ 5.00	€ 0.95	€ 5.95
Abbreviations: INH = inhalant, CIS = concentrate for the preparation of an infusion solution, SIJ = suspension for injection, IIS = injection/ infusion solution				

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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.

Isoflurane is administered exclusively via the Sedaconda Anaesthetic Conserving Device (ACD) application system and the Sedaconda syringe. The ACD must be replaced every 24 hours. The hospital may incur additional costs for the application system and the Sedaconda syringe. These additional costs related to medicinal treatment, such as equipment or consumables are reimbursed within the framework of the flat-rate inpatient reimbursement system in SHI and cannot be quantified at this point.

[4] The costs of the medicinal products are reimbursed via the respectively applicable DRG case flat fees.

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 31 January 2022, the pharmaceutical company submitted a dossier for the benefit assessment of isoflurane to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 7 VerfO.

By letter dated 31 January 2022 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 isoflurane.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 April 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 2 May 2022. The deadline for submitting written statements was 23 May 2022.

The oral hearing was held on 7 June 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 12 July 2022, and the proposed resolution was approved.

At its session on 21 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 March 2021	Determination of the appropriate comparator therapy
Working group Section 35a	1 June 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 June 2022	Conduct of the oral hearing
Working group Section 35a	14 June 2022 21 June 2022 6 July 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	12 July 2022	Concluding discussion of the draft resolution
Plenum	21 July 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 July 2022

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

Prof. Hecken