IQWiG Reports – Commission No. A22-10

Isoflurane (sedation during mechanical ventilation) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Isofluran (Sedierung bei mechanischer Beatmung) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Isoflurane (sedation during mechanical ventilation) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
1 February 2022

Internal Commission No.
A22-10

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Leopold Eberhart, University Hospital of Gießen and Marburg, Marburg, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

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

IQWiG employees involved in the dossier assessment

- Erika Baumbach
- Reza Fathollah-Nejad
- Lisa Junge
- Florina Kerekes
- Annika Orland
- Sonja Schiller
- Anke Schulz
- Volker Vervölgyi

Keywords: Isoflurane, Conscious Sedation, Benefit Assessment, 2016-004551-67

Table of contents

List of tables[2]

Page

[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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICU	intensive care unit
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RASS	Richmond Agitation-Sedation Scale
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 isoflurane. 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 1 February 2022.

Research question

The aim of the present report is the assessment of the added benefit of isoflurane in comparison with the appropriate comparator therapy (ACT) in mechanically ventilated adult patients during intensive care for whom sedation is indicated.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of isoflurane

Therapeutic indication	**ACT[a]**
Sedation of mechanically ventilated adult patients in intensive care	Treatment of physician's choice under consideration of propofol, midazolam and dexmedetomidine
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

In principle, the company followed the G-BA's specification of the ACT, but stated that in the German health care context, propofol is usually the treatment of physician's choice. According to the company, the use of midazolam for sedation is no longer recommended and dexmedetomidine is only suitable for lower levels of sedation and is therefore only of secondary importance. The company based its argumentation on the German S3 guideline for the management of analgesia, sedation and delirium in intensive care medicine (DAS guideline) and on several standard operating procedures of various hospitals.

It can be inferred from the references cited by the company and the Summary of Product Characteristics (SPC) of propofol that propofol should be considered preferentially for a planned sedation duration of 7 days or less. For longer sedation, midazolam can be used, for example. Contrary to the argumentation of the company, the guideline no longer recommends the use of midazolam as a continuous infusion not in principle, but explicitly only for deep sedation due to the poor controllability and the risk of accumulation of parent drug and metabolites. However, midazolam can be used as part of a multimodal approach in bolus doses or in certain patient groups (e.g. patients with alcohol dependence or severe injuries). In addition, isoflurane is approved for all target sedation levels and thus also for light sedation, so

that dexmedetomidine can also be considered as a comparator therapy for patients with prescribed light sedation.

The assessment is conducted in comparison with the ACT specified by the G-BA and by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Study pool and study design

The check of completeness did not find any relevant study for assessing the added benefit of isoflurane in comparison with the ACT.

The company, in contrast, identified the randomized controlled trial (RCT) SED001 and used it in its assessment. The SED001 study is unsuitable for assessing the benefit of isoflurane versus the ACT. This is explained below.

Design of the SED001 study

The SED001 study is a randomized, open-label study comparing isoflurane with propofol. The study included mechanically ventilated adult patients who had received up to 48 hours of propofol for sedation before randomization. At the time of randomization, patients still had to have clinically probable indication for sedation for at least 24 hours with target sedation depth within the range of −1 (light sedation) to −4 (deep sedation) on the Richmond Agitation-Sedation Scale (RASS).

The study randomized a total of 301 patients at a 1:1 ratio to either sedation with isoflurane (N = 150) or sedation with propofol (N = 151).

Treatment with isoflurane and propofol was mostly in compliance with the respective SPC. According to the study protocol, in cases of inadequate sedation or acute agitation, bolus doses of the assigned study medication or (if the target sedation depth was not achieved with isoflurane or propofol) or midazolam were allowed (referred to as “rescue therapy” by the company).

Treatment with the study medication was limited to 48 hours (± 6 hours). Wake-up tests were carried out after 24 hours and after 48 hours, with the possibility of extubation, depending on the condition of the patients. After the end of the study treatment, patients still in need of sedation received standard local treatment. The observation period was up to 30 days, depending on the outcome.

The primary outcome of the study was the proportion of time over which the prescribed sedation level was maintained. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity and adverse events (AEs).

Based on the available information on the patients included in the SED001 study, it can be assumed that propofol was the treatment of physician’s choice for the patients at study entry. On the basis of the SED001 study, it would therefore be possible to draw conclusions about

patients for whom propofol represents a treatment of physician's choice. However, the study is not relevant for the present benefit assessment.

Limitation of the duration of treatment with the study medication not adequate

According to the inclusion criteria, patients in the SED001 study had to be clinically likely to require sedation for at least 24 hours at the time of randomization. The maximum duration of treatment with the study medication was 48 hours (± 6 hours). If sedation was indicated again after the end of treatment with the study medication or after a break, the patients received this according to local standards.

It can be inferred from the data provided by the company that a relevant proportion of the patients included in the study still had an indication for sedation after the treatment period with the study medication (48 hours ± 6 hours). This means that only part of the sedation period is represented for these patients, which means that conclusions on the added benefit for the comparison of isoflurane versus propofol as treatment of physician's choice are not possible. In addition, there are no substantive reasons for switching sedatives in a relevant proportion of patients, especially in the isoflurane arm. The benefit assessment would require data that cover the use of the study medication over the entire sedation period until extubation, including sufficiently long follow-up observation of patient-relevant outcomes (e.g. questionnaire on memories of the stay in the intensive care unit (ICU) or of sedation). The SED001 study is therefore unsuitable for the present benefit assessment.

Results

There are no suitable data for the assessment of the added benefit of isoflurane in comparison with the ACT in mechanically ventilated adult patients during intensive care for whom sedation is indicated. Hence, there is no hint of an added benefit of isoflurane in 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 shows a summary of the probability and extent of added benefit of isoflurane.

[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. Isoflurane – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Sedation of mechanically ventilated adult patients in intensive care	Treatment of physician's choice under consideration of propofol, midazolam and dexmedetomidine	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of isoflurane in comparison with the ACT in mechanically ventilated adult patients during intensive care for whom sedation is indicated.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of isoflurane

Therapeutic indication	**ACT[a]**
Sedation of mechanically ventilated adult patients in intensive care	Treatment of physician's choice under consideration of propofol, midazolam and dexmedetomidine
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

In principle, the company followed the G-BA's specification of the ACT, but stated that in the German health care context, propofol is usually the treatment of physician's choice. According to the company, the use of midazolam for sedation is no longer recommended and dexmedetomidine is only suitable for lower levels of sedation and is therefore only of secondary importance. The company based its argumentation on the German S3 guideline for the management of analgesia, sedation and delirium in intensive care medicine (DAS guideline) [3] and on several standard operating procedures of various hospitals [4-21].

It can be inferred from the references cited by the company and the SPC of propofol [22] that propofol should be considered preferentially for a planned sedation duration of 7 days or less. For longer sedation, midazolam can be used, for example. Contrary to the argumentation of the company, the guideline no longer recommends the use of midazolam as a continuous infusion not in principle, but explicitly only for deep sedation due to the poor controllability and the risk of accumulation of parent drug and metabolites. However, midazolam can be used as part of a multimodal approach in bolus doses or in certain patient groups (e.g. patients with alcohol dependence or severe injuries). In addition, isoflurane is approved for all target sedation levels and thus also for light sedation, so that dexmedetomidine can also be considered as a comparator therapy for patients with prescribed light sedation.

The assessment is conducted in comparison with the ACT specified by the G-BA and by means of patient-relevant outcomes on the basis of the data provided 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 of the company in the dossier:

- study list on isoflurane (status: 1 November 2021)

- bibliographical literature search on isoflurane (last search on 1 November 2021)
- Search in trial registries/trial results databases for studies on isoflurane (last search on 1 November 2021)
- Search on the G-BA website for isoflurane (last search on 1 November 2021)

To check the completeness of the study pool:

- bibliographic literature search on isoflurane (last search on 9 March 2022); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on isoflurane (last search on 17 February 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any relevant studies for assessing the added benefit of isoflurane in comparison with the ACT.

The company, in contrast, identified the RCT SED001 [23-25] and used it in its assessment. The SED001 study is unsuitable for assessing the benefit of isoflurane versus the ACT. This is explained below.

Evidence provided by the company

Design of the SED001 study

The SED001 study is a randomized, open-label study comparing isoflurane with propofol. The study was conducted in Germany and Slovenia. The study included mechanically ventilated adult patients who had received up to 48 hours of propofol for sedation before randomization. At the time of randomization, patients still had to have clinically probable indication for sedation for at least 24 hours with target sedation depth within the range of −1 (light sedation) to −4 (deep sedation) on the RASS. Patients who had not reached the prescribed target sedation depth at any time during the 8 hours before randomization were excluded from the study.

The study randomized a total of 301 patients at a 1:1 ratio to either sedation with isoflurane (N = 150) or sedation with propofol (N = 151). Randomization was stratified by study centre.

Patients in the intervention arm received isoflurane inhalation via the Sedaconda delivery system; patients in the comparator arm received intravenous propofol at a concentration of 2%. According to the study protocol, in cases of inadequate sedation or acute agitation, bolus doses of the assigned study medication or (if the target sedation depth was not achieved with isoflurane or propofol) or midazolam were allowed (see Table 11 of the full dossier assessment). The use of other sedatives was not considered a protocol violation if they were used as standard therapy. The additional administration of bolus doses of sedatives was called “rescue therapy”.

Treatment with isoflurane and propofol was mostly in compliance with the respective SPC [22,26]. The SPC does not recommend possible administration of bolus doses of propofol for the propofol concentration used in the study (2%). It is not clear from the data provided by the company how many patients in the propofol arm received bolus doses of propofol. In the isoflurane arm, 7 patients received at least 1 bolus of propofol on day 1 and 6 patients received at least 1 bolus of propofol on day 2 (it is unclear whether some of these were the same patients).

Treatment with the study medication was limited to 48 hours (± 6 hours). Wake-up tests were carried out after 24 hours and after 48 hours, with the possibility of extubation, depending on the condition of the patients. After the end of the study treatment, patients still in need of sedation received standard local treatment. The observation period was up to 30 days, depending on the outcome. This observation period (7 or 30 days, see Table 12 of the full dossier assessment) was added as part of a protocol amendment after 150 patients had already been included in the study. For most of these patients, retrospective consent could be obtained for this observation period; but for some patients, no data are available for this observation period, so they were only followed up for 24 hours (27 patients in the isoflurane arm and 21 patients in the propofol arm, see also Table 12 of the full dossier assessment).

The primary outcome of the study was the proportion of time over which the prescribed sedation level was maintained. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity and AEs.

Further details on the characteristics of the SED001 study, the interventions used in the study, and the patients included can be found in Appendix B of the full dossier assessment.

Based on the available information on the patients included in the SED001 study (Table 12 of the full dossier assessment), it can be assumed that propofol was the treatment of physician's choice for the patients at study entry. On the basis of the SED001 study, it would therefore be possible to draw conclusions about patients for whom propofol represents a treatment of physician's choice. However, the study is not relevant for the present benefit assessment (see following section).

Limitation of the duration of treatment with the study medication not adequate

According to the inclusion criteria, patients in the SED001 study had to be clinically likely to require sedation for at least 24 hours at the time of randomization. The maximum duration of treatment with the study medication was 48 hours (± 6 hours). If sedation was indicated again after the end of treatment with the study medication or after a break, the patients received this according to local standards. It is questionable whether switching sedatives for no apparent reason is consistent with the health care context.

It is not clear from the data provided by the company how many patients were sedated beyond the period of treatment with the study medication. The available documents provide only information on the most frequently used concomitant treatments within the first 24 hours after

the end of treatment with the study medication. 110 patients in each study arm had received at least one concomitant medication during this period. Of these, in the isoflurane arm, 19% received isoflurane, 14% propofol and 13% clonidine; in the propofol arm, propofol was most frequent (27%), 14% received clonidine and 4% isoflurane. A partial overlap of the administration of the sedatives mentioned can be assumed, as boluses may also have been administered with one sedative ("rescue therapy"), while continuous sedation was administered with another sedative. The proportions can therefore not be added up. Furthermore, there is no information available on all sedatives administered. Nevertheless, it can be derived from the available data that a relevant proportion of patients continued to be sedated immediately after the end of treatment with the study medication. It remains unclear over which period of time these patients were sedated continuously (without taking into account the wake-up tests) or whether the sedative administered until then was switched in the period after the 24 hours after the end of treatment with the study medication (from hour 73 after randomization). From the analyses of the outcome of duration of ventilation, which included 117 patients in the isoflurane arm and 123 in the propofol arm, it can be inferred that a relevant proportion of patients were ventilated beyond the duration of treatment with the study medication. For example, 20% of patients had a maximum of 2 ventilator-free days during the entire 30-day study period. As a rule, there is a correlation between mechanical ventilation and sedation indication [3], so that it can be assumed that a relevant proportion of the ventilated patients were sedated for a notably longer period beyond the period of treatment with the study medication. This is also supported by the fact that only 55 of the patients in the isoflurane arm and 63 of the patients in the propofol arm had been extubated by the end of treatment with the study medication. For the remaining patients who had not died by then (within the first 72 hours after randomization, 3 patients had died in each of both arms), it can be assumed that there was still an indication for ventilation and thus mostly also for sedation.

With regard to the 30-day observation period, no information is available on the therapy used after the end of treatment with the study medication, except for information on switching to the respective other treatment (switching to propofol in the isoflurane arm, switching to isoflurane in the propofol arm): 42% of the patients in the isoflurane arm and 14% in the propofol arm received sedation with the respective other sedative during the 30-day observation period. The percentages here refer to the number of patients for whom corresponding data are available in the 30-day period (121 patients in the isoflurane arm and 129 patients in the propofol arm). The available data do not provide any information on whether or not there were longer sedation breaks in between.

Since a relevant proportion of patients still had an indication for sedation after the 48-hour treatment period, the predefined treatment period with the study medication of 48 ± 6 hours only covers part of the actual sedation period for some patients. The fact that after the end of the study medication, patients were switched to the standard local therapy is also problematic, especially in the isoflurane arm, since according to the SPC, sedation with isoflurane is not limited to a certain period of time [26]. However, it can be assumed that a relevant proportion

of patients with a continuing indication for sedation were switched to another sedative (see above). There are no substantive reasons for limiting the duration of treatment with the study medication to a maximum of 54 hours and subsequently switching sedatives according to local standard. The SED001 study is therefore unsuitable for the present benefit assessment. The benefit assessment would require data that cover the use of the study medication over the entire sedation period until extubation, including sufficiently long follow-up observation of patient-relevant outcomes (e.g. questionnaire on memories of the stay in the ICU or of sedation). Especially for the outcomes of all-cause mortality and AEs, a follow-up observation of at least 28 days after the end of sedation or after extubation seems adequate.

Regardless of the unsuitability of the SED001 study for the present benefit assessment, only the outcome of awakening showed a statistically significant result. The outcome is defined as the time from stop of continuous sedation to the time RASS ≥ 0 is reached during a wake-up test. A statistically significant difference between the treatment arms was only shown for the second wake-up test (after 48 hours). However, fewer than half of the randomized patients were included in the analysis. However, this cannot be explained by the fact that many patients had already been extubated by this time. In addition, the analysis presented by the company on the time to wake-up only reflects the controllability of sedation and it is unclear to what extent a long or short time to wake-up reflects a patient-relevant benefit.

Conclusion

The study SED001 included by the company for the benefit assessment investigated a sedation period with the study medication of 48 hours (± 6 hours). It can be inferred from the data provided by the company that a relevant proportion of the patients included in the study still had an indication for sedation after the treatment period. This means that only part of the sedation period is represented for these patients, which means that conclusions on the added benefit for the comparison of isoflurane versus propofol as treatment of physician's choice are not possible. In addition, there are no substantive reasons for switching sedatives in a relevant proportion of patients, especially in the isoflurane arm. The SED001 study is therefore unsuitable for the present benefit assessment.

2.4 Results on added benefit

There are no suitable data for the assessment of the added benefit of isoflurane in comparison with the ACT in mechanically ventilated adult patients during intensive care for whom sedation is indicated. Hence, there is no hint of an added benefit of isoflurane in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of isoflurane in comparison with the ACT.

Table 5: Isoflurane – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Sedation of mechanically ventilated adult patients in intensive care	Treatment of physician's choice under consideration of propofol, midazolam and dexmedetomidine	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of non-quantifiable added benefit based on SED001 study.

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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. General Methods; Version 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI), Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI). S3-Leitlinie; Analgesie, Sedierung und Delirmanagement in der Intensivmedizin (DAS-Leitlinie 2020) [online]. 2021 [Accessed: 22.03.2022]. URL: https://www.awmf.org/uploads/tx_szleitlinien/001-012l_S3_Analgesie-Sedierung-Delirmanagement-in-der-Intensivmedizin-DAS_2021-08.pdf.

4. B. G. Klinikum Duisburg. Standard Analgosedierung auf der Intensivstation. 2018.

5. Elisabeth Krankenhaus Dorsten. SOP Inhalative Sedierung. 2019.

6. Ev K Castrop-Rauxel. SOP Analgosedierung auf der Intensivstation. 2018.

7. Flensburger Kliniken. Flensburger Leitlinien für die Anästhesie. 2018.

8. S LK-Kliniken Heilbronn GmbH. SOP Analgesie und Sedierung. 2018.

9. Helios Klinikum Erfurt. SOP Analgosedierung [online]. 2019 [Accessed: 03.11.2021]. URL: https://www.helios-gesundheit.de/kliniken/erfurt/unser-angebot/unsere-fachbereiche/anaesthesie/fortbildung-lehre-forschung-sops/sops-der-kans/analgosedierung/.

10. Kliniken Nordoberpfalz AG. Verfahrensanweisung Analgosedierung beim intubierten Patienten. 2019.

11. S. L. K. Kliniken. Zentrum für AINS, Klinikum am Gesundbrunnen. Verfahrensanweisung Analgosedation. 2021.

12. Klinikum Memmingen. SOP Analgesie, Sedierung und Delirmanagement. 2020.

13. Klinikum Westmünsterland. Verfahrensanweisung Analgosedierung. 2017.

14. Schwarzwald-Baar Klinikum. Klinik für Anästhesiologie, Intensiv-, Notfall- und Schmerzmedizin. SOP Sedierung auf ICU. 2020.

15. St Marienkrankenhaus Ludwigshafen. Analgosedierung Operative Intensivstation. 2019.

16. Stiftung Hospital Zum Heiligen Geist. Verfahrensanweisung Sedierung, Delir, Schmerz, Agitation. 2021.

17. Universitätsklinikum Düsseldorf. Verfahrensanweisung Sedierung, Analgesie und Delirmanagement. 2019.

18. Universitätsklinikum des Saarlands. Arbeitsanweisung Analgesie, Sedierung und Delirtherapie. 2019.

19. Universitätsklinikum Regensburg. Analgosedierung beim intubierten Patienten [online]. 2009 [Accessed: 03.11.2021]. URL: https://www.ukr.de/imperia/md/content/kliniken-institute/innere-medizin-i/sops/intensiv-undnotfallmedizin/nt-anal.pdf.

20. Universitätsmedizin Mainz. SOP Intensivmedizinische Therapie bei SARS-CoV-2-Infektion und COVID-19 Erkrankung [online]. 2020 [Accessed: 03.11.2021]. URL: https://www.dgai.de/alle-docman-dokumente/aktuelles/1303-sop-intensivtherapie-bei-sars-cov-2-und-covid-19-version-1-4/file.html.

21. Vivantes Klinikum Spandau. SOP Analgosedierung. 2021.

22. Aspen. Disoprivan 2 % [online]. 2020 [Accessed: 22.03.2022]. URL: https://fachinfo.de.

23. Sedana Medical AB. A randomised, controlled, open-label study to confirm the efficacy and safety of sedation with isoflurane in invasively ventilated ICU patients using the AnaConDa administration system [online]. [Accessed: 01.03.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-004551-67.

24. Sedana Medical AB. A randomised, controlled, open-label study to confirm the efficacy and safety of sedation with isoflurane in invasively ventilated ICU patients using the AnaConDa administration system, The IsoConDa study; study SED001; clinical study report [unpublished]. 2020.

25. Meiser A, Volk T, Wallenborn J et al. Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomised controlled, non-inferiority trial. Lancet Respir Med 2021; 9(11): 1231-1240. https://dx.doi.org/10.1016/s2213-2600(21)00323-4.

26. Sedana Medical AB. Sedaconda 100 % V/V Flüssigkeit zur Herstellung eines Dampfs zur Inhalation [online]. 2021 [Accessed: 07.04.2022]. URL: https://sedanamedical.com/media/0s0a5dng/spc-sedaconda-germany.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-10.html.